I. SYNTHESIS ON TEMPLATES : THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE

II. COMPETING PATHWAYS IN TEMPLATE SYNTHESIS : ALKALI MEDIATED RING-RING TRANSFORMATIONS IN 4-QUINAZOLONES

by

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DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

DECEMBER, 1985

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A Thesis Submitted
in Partial Fulfilment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

FIRDOUS FAROOQI

to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY KANPUR

DECEMBER, 1985

"Nothing ventured, nothing gained,"
We're sure to prove this true
If we expect a harvest
But think there is naught to do.

Argue
for your limitations
and sure enough,
they're
yours

VISHAL

Dedicated

to

My Parents

CERTIFICATE

Certified that the work contained in this thesis, entitled, "SYNTHESIS ON TEMPLATES: THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE; COMPETING PATHWAYS IN TEMPLATE SYNTHESIS RING-RING TRANSFORMATIONS IN 4-QUINAZOLONES" has been carried out by Miss Firdous Farooqi under my supervision and the same has not been submitted elsewhere for a degree.

S. Ranganathan

(S. Ranganathan)
Thesis Supervisor

Kanpur

December, 1985

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Kanpur, India, under the supervision of Professor S.Ranganathan.

In keeping with the general practice of reporting scientific observations due acknowledgements have been made wherever the work embodied is based on the findings of other investigators.

Firdous Farooqi

Firdous Farooqi

CERTIFICATE

Certified that the work contained in this thesis, entitled, "SYNTHESIS ON TEMPLATES· THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE; COMPETING PATHWAYS IN TEMPLATE SYNTHESIS RING-RING TRANSFORMATIONS IN 4-QUINAZOLONES" has been carried out by Miss Firdous Farooqi under my supervision and the same has not been submitted elsewhere for a degree.

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DEPARTMENT OF CHEMISTRY

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CERTIFICATE OF COURSE WORK

This is to certify that Miss Firdous Farooqi has satisfactorily completed all the course requirements for the Ph.D. degree programme. The courses include:

Chm 502	Advanced Organic Chemistry
Chm 505	Principles of Organic Chemistry
Chm 524	Modern Physical Methods
Chm 525	Principles of Physical Chemistry
Chm 545	Principles of Inorganic Chemistry
Chm 581	Basic Biological Chemistry
Chm 801	Graduate Seminar
Chm 900	Research
Chm 800	General Seminar

Miss Firdous Farooqi has successfully completed her qualifying examinations in August 1983.

P T Narasimhan 10/12/85

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Professor and Head
Department of Chemistry

P C Nigam

(P.C. Nigam)
Convenor
Department of Post
Graduate Committee

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Firdous Farooqi

PREFACE

ORGANIZATION

The thesis entitled 1. SYNTHESIS ON TEMPLATES: THE CHEMICAL SIMULATION OF THE ATP-IMIDAZOLE CYCLE. II. COMPETING PATHWAYS IN TEMPLATE SYNTHESIS: ALKALI MEDIATED RING-RING TRANSFORMATIONS IN 4-QUINAZOLONES consist of, for each part, five sections, namely, A. Introduction, B. Background, C. Present Work, D. Spectra and E. Experimental.

SUMMARY OF THE PRESENT WORK

A unique example of template strategy in Nature is the ATP-imidazole cycle wherein a daughter imidazole is grown on a mobile parent imidazole *via* a cyclic pathway that is linked to the biosynthesis of the purine code bases ATP and GTP as well as to the imidazole amino acid histidine. The cycle is initiated by the parent, namely, protected 5-amino imidazole 4-carboxamide by acceptance of elements of formic acid to give 9-protected hypoxanthine. This is aminated to adenine and then to, *via* sequence, specific 1N-incorporation of ribose phosphate, hydrolysis, Amadori rearrangement, enamination, cyclization and cleavage to the daughter histidine precursor and the parent imidazole template that now can initiate

another cycle.

The chemical simulation of the salient features of the ATP-Imidazole cycle has been accomplished as a result of protracted endeavours. The ultimate objective was realised in stages of increasing complexity and sophistication.

The chemical simulation of the ATP-Imidazole cycle was initially carried out on a model which possessed the operating part of the cycle, namely, the vicinal disposition of the $-NH_2$ and $-CONH_2$ units and substituting the more reactive imidazole moiety with a phenyl ring. Thus, all early experiment made use of anthranilamide (2)* rather than the N-substituted 5-aminoimidazole 4-carboxamide (1) as the template.

The strategy that led to the successful demonstration of anthranilamide (2) as a template for imidazole synthesis proceeded through the sequence, transformation to 4-quinazolone (4), specific alkylation at the 3-location with either phenacyl bromide or bromoacetone reaction with a primary amine leading to the formation of the daughter imidazole and the modified parent, which could be transformed to 2, to start another cycle.

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*These numbers refer to those presented in the thesis, Sections I.C. and II.C.

Specific 3N-alkylation of 4-quinazolone (4) was achieved by treatment of its conjugate base - generated with 1 equivalent of KOH — with phenacyl bromide in ethanol to give, in 40% yields 3-phenacyl 4-quinazolone (6). By a similar procedure 3-acetonyl 4-quinazolone (7) was prepared using bromoacetone in 50% yields. Compound 6 proceeded through the cycle on reflux for 12 hours with benzylamine (4 equivalents) and p-TsOH (2 equivalents) leading to the template product 1-benzyl 5-phenyl imidazole (8) in 69% yields and anthranilbenzylamide (10) in 71% yields. The latter was transformed to the template, anthranilamide (2) in 85% yields by treatment with methenesulphonic acid. Thus, the sequence of events, represents synthesis of an imidazole on the template anthranilamide. In an analogous manner, 3-acetonyl 4-quinazolone (7) was transformed to 1-benzyl 5-methyl imidazole (9, 55%, overall yield from anthranilamide 23.6%) and the amide 10 (45%).

The selective formation of specifically 5-substituted N-protected imidazoles by the template strategy provides the best route to such compounds.

The general utility of the template strategy for the preparation of 1-protected 5-substituted imidazoles as well as for a variety of 1-substituted imidazoles has been further established.

The reaction of 6 with octadecylamine in refluxing xylene, promoted by p-TsOH, gave the daughter product, 1-octadecyl 5-phenyl imidazole (11, 32%) with simultaneous formation of the anthranil octadecyl amide (13, 35%). In an analogous manner compound 7 when processed through the cycle gave 1-octadecyl 5-methyl imidazole (12, 18%) and 31% of 13. The novel lipids 11 and 12 are of interest since they carry the biologically important imidazole unit.

1-Cyclohexyl 5-phenyl imidazole (14, 70%) and anthranilcyclohexyl amide (15, 65%) were obtained when 6 was processed through the cycle with cyclohexyl amine.

The cyclic operations with anthranilamide illustrate that aspect of the ATP-Imidazole cycle which involves the directed synthesis of an imidazole using a soluble template. Another facet of the Natural cycle which is aesthetically more pleasing, is the generation of a daughter imidazole from a parent imidazole template. This has been accomplished starting from 1-benzyl 5-amino imidazole 4-carboxamide (1).

1-Benzyl 5-aminoimidazole 4-carboxamide (1) was transformed to 9-benzyl hypoxanthine (3) by treatment with formamide in 87% yields. Specific 1N-alkylation of 3 was accomplished by treatment of its potassium salt-formed *in situ* with 1 equivalent of KOH in EtOH - with phenacyl bromide to give 1-phenacyl 9-benzyl hypoxanthine (16, 82%). Compound 16 on treatment with 4 equivalents of benzylamine in refluxing xylene for 12 hours in presence of 3 equivalents of p-TsOH

gave 36% of the daughter product 1-benzyl 5-phenyl imidazole (8) and 5-amino 1,N-dibenzylimidazole 4-carboxamide (17, 33%). Reaction of 17 with neat methane sulfonic acid at 125-130°C for 3 hours gave in 80% yield the parent template 1, which was available to initiate the second cycle.

1-Benzyl 5-aminoimidazole 4-carboxamide (1) in an analogous manner was transformed, via 3 to the corresponding 1-acetonyl 9-benzyl hypoxanthine 18 (66%) by treatment with bromoacetone and then processed through the cycle leading to the derived product, 1-benzyl 5-methyl imidazole (9, 30%) and 5-amino 1,N-dibenzyl imidazole 4-carboxamide (17, 26%).

In the ATP-Imidazole cycle the derived imidazole is transformed to histidine. In the present work this has been simulated. Selenium dioxide oxidation of 9 followed by $NaBH_4$ reduction of the resulting aldehyde gave 1-benzyl 5-hydroxy methyl imidazole. This on deprotection ($Pd/C/H_2$), reaction with $SOCl_2$, followed by alkylation with sodio-acetamidomalonic ester and hydrolysis gave dl-histidine, identical in all respects with an authentic sample.

The cyclic template strategy leading to derived imidazoles has also been illustrated with adenine, an actual participant in the natural ATP-Imidazole cycle.

The reaction of 9-benzyladenine (19) with phenacyl-bromide in dry DMF at rt. gave, surprisingly, the bis-salt 20.

Compound 20 on treatment with hot water gave the monohydrobromide 21. Compound 21 when held at reflux in xylene for 4 hours with 4 equivalents of benzylamine gave a 38% yield of the daughter product 1-benzyl 5-phenyl imidazole (8). In addition, there was obtained a crystalline compound, for which, based on spectral and analytical data, structure 22 has been assigned (28%).

Compound 22 when refluxed in xylene with 4 equivalents of benzylamine and 1 equivalent of p-TsOH for 12 hours gave an excellent (88%) yield of the template product 1-benzyl 5-phenyl imidazole (8), thus demonstrating that the earlier conjecture to the effect that the template operations proceed *via* key enamine intermediate has much substance.

In practice, the intermediate 22 can be bypassed by treatment of 21 with benzylamine and p-TsOH in refluxing xylene leading directly to derived imidazoles. Thus, 21 on reflux in dry xylene with $PhCH_2NH_2$ (4 equivalents) and p-TsOH (2 equivalents) for 12 hours followed by work up gave 71% of the derived product 8; with cyclohexylamine under the same conditions, 1-cyclohexyl 5-phenyl imidazole was obtained in 50% yields.

Unlike 9-benzyladenine 19, the related 4-amino quinazoline (23) failed to yield an imidazole derivative. Treatment of 4-aminoquinazoline (23) with phenacyl bromide (1.5 equivalents) in dry DMF at room temperature and work up as described for 20, gave the 3N-monoalkylated salt 24, in 68% yields. The use of 24 as a template for imidazoles was foiled because of preference for Dimroth rearrangement giving rise to 25, in 77% yields (CHART I.S.4). The reaction of 25 with benzylamine (4 equivalents) and p-TsOH (2 equivalents) in refluxing xylene for 12 hours gave 4-benzylamino quinazoline (26) in 56% yields. Treatment of 24 with $PhCH_2NH_2$ and p-TsOH in hot xylene gave none of the expected derived imidazoles.

The successful demonstration using appropriate molecular moulds for the production of daughter molecules represents a new strategy in organic synthesis, but not one that is alien to Nature. Such template syntheses allows wide variations in terms of the parent template, the steps involved in the cyclic operation and the nature of the derived molecules.

An important step in the ATP-Imidazole cycle is the hydrolytic cleavage of an alkylated adenine, resulting in the regeneration of the template amide grouping. A similar pathway with the model system, 3-substitute 4-quinazolones, would result in the hydrolytic rupture of the 3,4-bond.

However, all such endeavours, which is the focus of the present work, did not succeed. Nevertheless these studies are noteworthy in that they have led to the demonstration of subtle, interesting and novel properties of these compounds.

The reaction of 3-phenacyl 4-quinazolone (6) in refluxing 0.4N NaOH gave anthranilic acid (45, 45%) and 3-amino 2,4 diphenyl pyrrole (46, 31%). The reaction thus resulted in the cleavage of the 1,2 and 3,4-bond of 6 leading to 45 and ω-amino acetophenone, which on dimerization and loss of water yielded the pyrrole 46.

To steer the system from proclivity for 2,3 cleavage, the 2-blocked compound, 2-methyl 3-phenacyl 4-quinazolone (38) was prepared. The action of dilute alkali on 38 gave in quantitative yields, the novel aromatic tricyclic system 54, via compound 53, demonstrating that this reaction is entirely controlled by the conjugate base of the 2-methyl grouping thus effectively precluding the 1,2 and 3,4-bond cleavage as well as intramolecular enolate addition. This propensity was entirely curbed with 2-methyl 3-benzamido 4-quinazolone (56) which on treatment with dilute alkali gave only the triazole 57, arising from the expected 3,4-bond cleavage and the unwanted subsequent cyclization involving the 1N position. The latter tendency could not be overcome with 2-phenyl 3-benzamido 4-quinazolone (61), which again gave on

reaction with dilute alkali, the triazole 63. Compound 61 underwent hydrolytic cleavage in distilled water at 200°C leading to a multitude of products arising from the 3,4-bond cleavage.

Thus, the hydrolytic experiments led to practically every possible mode of cleavage, an important exception being the formation of the anticipated derived product namely, 2,5-diphenyl oxadiazole.

CONTENTS

CHAPTER I

SYNTHESIS ON TEMPLATES: THE CHEMICAL SIMULATION OF ATP-IMIDAZOLE CYCLE

I.A. INTRODUCTION

The ATP-Imidazole cycle represents a unique synthetic strategy of Nature. In this process, N-protected 5-amino-imidazole 4-carboxamide serves as a soluble template, in a cyclic process, leading to a daughter imidazole 5-glycerol phosphate — which is then transformed to histidine—and the template which could start another cycle.

The chemical simulation of the salient features of the ATP-Imidazole cycle has been accomplished as a result of protracted endeavours. The ultimate objective was realised in stages of increasing complexity and sophistication.

The concept of the template strategy inherent in the ATP-Imidazole cycle and centred around the vicinal disposition of —NH_2 and —$CONH_2$ functions has been successfully

transplanted to a more practical anchor. Thus, anthranilamide has been demonstrated as an excellent template for the synthesis of a range of N-protected 5-substituted imidazoles which are usually obtained by involved procedures. The protocol here is, transformation to 4-quinazolone with DMF-acetal, specific 3-N-alkylation with appropriate ligands, enamine formation with primary amines, cyclization and separation of the daughter from the parent, assisted by p-TsOH.

In the second stage, the N-protected 5-aminoimidazole 4-carboxamide template has been successfully used to generate the daughter imidazole *via* transformation to hypoxanthine and a sequence similar to that described above with anthranilamide. In this effort, the daughter 1-benzyl-5-methyl imidazole was transformed to dl-histidine involving a novel SeO_2 oxidation.

Finally, the multi-functional system adenine itself has been used as a template to generate daughter imidazole as is the case in the Natural ATP-Imidazole cycle. As anticipated, alkylations here were comparatively complex. However, these endeavours not only provided daughter imidazole but also led to the isolation and characterization of an unusual parent-daughter complex which could be transformed to the template products. The characterization of this complex provides an insight into the mechanism involved in these template operations.

The successful outcome of endeavours pertaining to the simulation of the salient features of the ATP-Imidazole cycle has brought to focus the usefulness of structural units possessing vicinally disposed $-NH_2$ and $-CONH_2$ functions or their equivalents, and anchored onto diverse ring systems, as possible parents for template synthesis. With this objective information relating to such systems in literature has been collated for the first time and presented as appropriate background for the present work in the following section (SECTION I.B).

I.B. BACKGROUND

RING FORMING REACTIONS OF ENE-AMINOACIDS:

The ene-aminoacid unit is a readily available structural element widely affixed to aromatic and heterocyclic rings. The vicinally aligned functional groups of such systems enable the formation of diverse structural types of considerable importance. A comprehensive account of the properties of such systems and an analysis of the potential of these in template synthesis form the subject matter of this section[1].

1. RING FORMING REACTIONS OF ANTHRANILIC ACID:

1.1 BENZOXAZONES:

Anthranilic acid (I) is transformed to benzoxazones either with carboxylic acids or their equivalents. The resulting compounds possess an active carbonyl function and consequently are used for the preparation of a variety of heterocyclic systems.

The reaction of compound I with carbonyl compounds resultsin the formation of dihydrobenzoxazones.

The formation of benzoxazones involving two units of I and brought about with CH_3SO_2Cl constitutes an interesting

reaction[13].

The type of the reaction and the nature of the products obtained are presented in TABLE.A.

1.2 ISATOIC ANHYDRIDES:

The reaction of I with derivatives of carbonic acid results in the formation of compounds called isatoic anhydrides, which are essentially cyclic carbamates. These compounds can effectively be used as starting materials for a range of heterocyclic compounds. The parent system can also be nitrated in good yields. The isatoic anhydrides can also be prepared in an indirect manner either by treatment with N, N-dimethyl carbamyl chloride in pyridine or via urethane formation and cyclization. A variety of N-substituted isatoic anhydrides could be prepared by Schiff bases derived either from I or its derivatives followed by reduction and reaction with ethyl chloroformate. The reaction of I with thioketene dimer[19] results in the formation of an analog of this system. These reactions are summarised in TABLE.B.

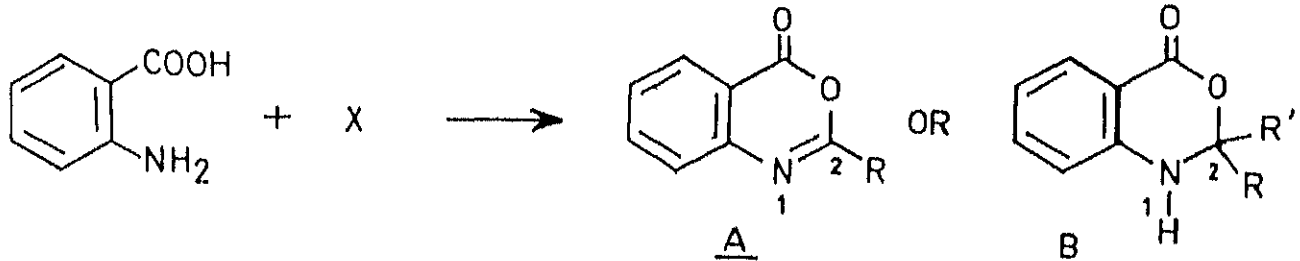
1.3 QUINAZOLONES:

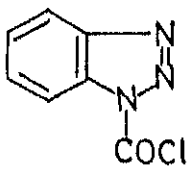
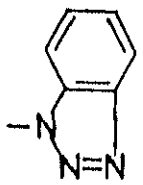
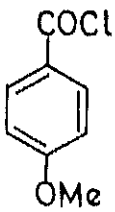
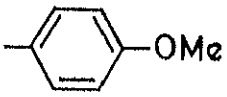
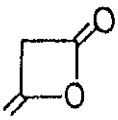
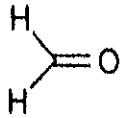
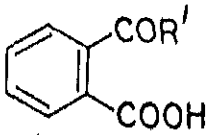
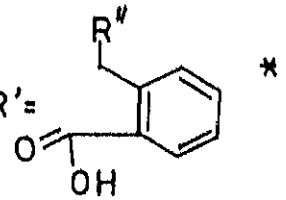
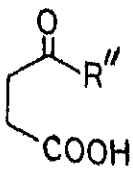
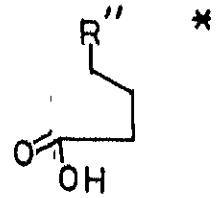
1.3.1 Formation of quinazolones from I and formamides:

The most simple method for the construction of a ring system from I is to interact the ene-aminoacid function with

TABLE A

REACTION TYPE

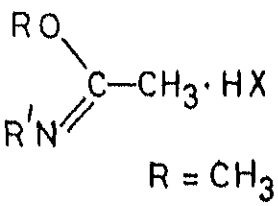
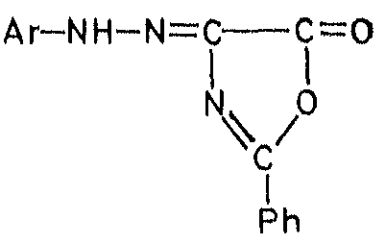
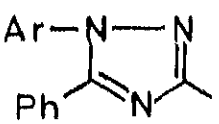
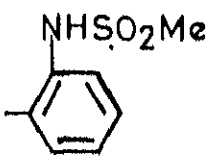
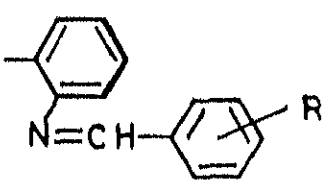
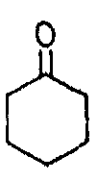
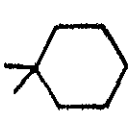


X	RING	R	Ref.
	A		2
$R'NCO$ $R' = Et, Ph$	A	$-NR'-\overset{O}{\overset{\|}{C}}-NHR'$ or = NR'	3
	A		4
	A	$-CH_2COCH_3$	5
$C_6H_{11}COCl$	A	$-C_6H_{11}$	6
	B	$R = R' = H$	7
 $R' = CH_3, Ph$	B	R, R'=  *	7
 $R = CH_3, Ph$	B	R, R'=  *	7

(contd)

TABLE A

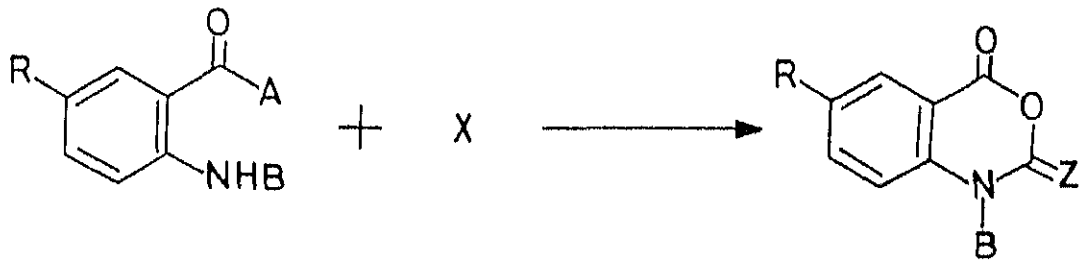
REACTION TYPE (contd)

X	RING	R	Ref.
$R^1R^2N^+{=}CCl_2Cl^-$	A	$-NR^1R^2$	8
$(R-\overset{O}{\overset{\|\|}{C}}-O)_2O$	A	$-R$	9
 $R = CH_3$	A	CH_3	10
CCl_3CHO	B	$R = -CCl_3$, $R' = H$	11
	A		12
$MeSO_2Cl$	A		13
$RC_6H_4CH{=}NC_6H_4COCl{-}O$	A		14
Me_2SO_4 , CH_2O	B	$R = R' = H$; 1—Me	15
	B	$R{=}R'{=}$ 	16

* Undergoes further cyclization

TABLE B

REACTION TYPE



R	A	B	X	Z	Ref.
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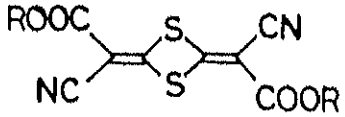
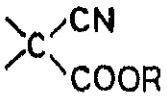
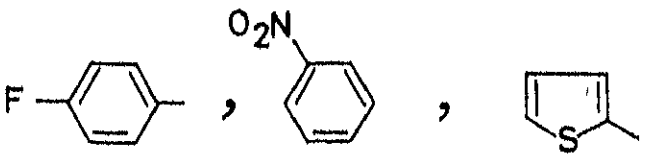
H	OH	H	$Me_2N-COCl$	O	18
H	OH	H			19
	OCH_3				
	NH_2				
Me	OH	CH_2R'	$ClCO_2Et$	O	20

R′ = 

formamides or their equivalents which carry a complementary functionality. Thus a variety of quinazolones arise by reaction of I with formamides. The versatility of this reaction is best illustrated with the ready formation of tricyclic heterocycles by reaction with isoxazolidones[24] and cyclic lactam ethers[25]. The reaction type is illustrated in TABLE.C.

1.3.2 Synthesis of quinazolones from I and thioformamides:

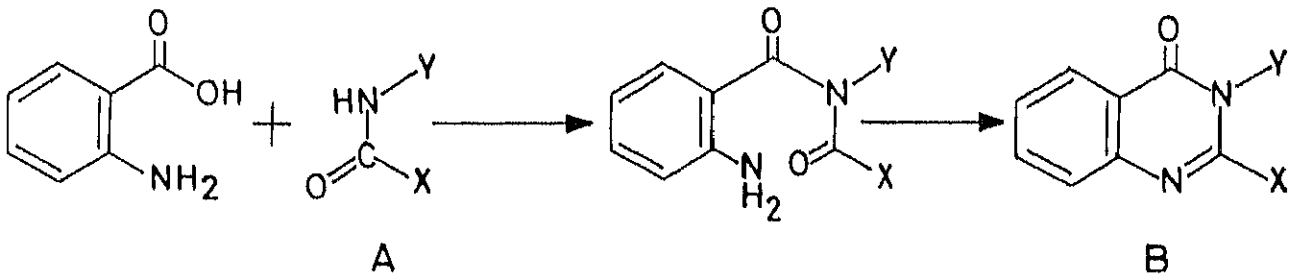
The appreciably enhanced reactivity of thioformamides enables the ready preparation of a variety of quinazolones from I. The reaction of 2,2'-dipyridylthioformamide with I leading to quinazolones with exceptional complex forming capabilities, is noteworthy[27]. Of interest is also the formation of tricyclic systems with 2-oxo 4-thiazolidones[28] (TABLE.D).

1.3.3 The preparation of quinazolones from acylated anthranilic acid (I) and amines:

In the earlier two types, synthons with capabilities of forming the 1,2 and 3,4 bonds of the quinazoline system were used. The needed bond formation could also be carried out frequently and usually starting with acylation of the amino unit of I followed by reaction with the appropriate primary amine system. The versatility and controls in this procedure are, as expected, better (TABLE.E).

TABLE C

REACTION TYPE



A

B

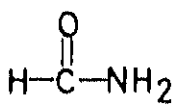
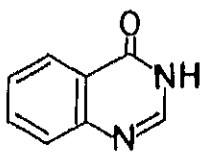
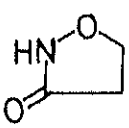
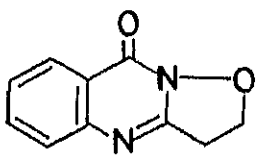
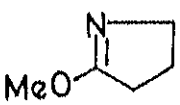
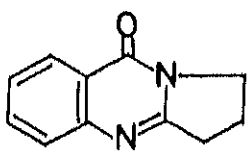
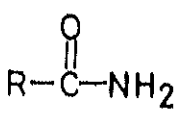
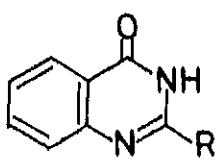
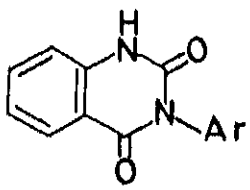
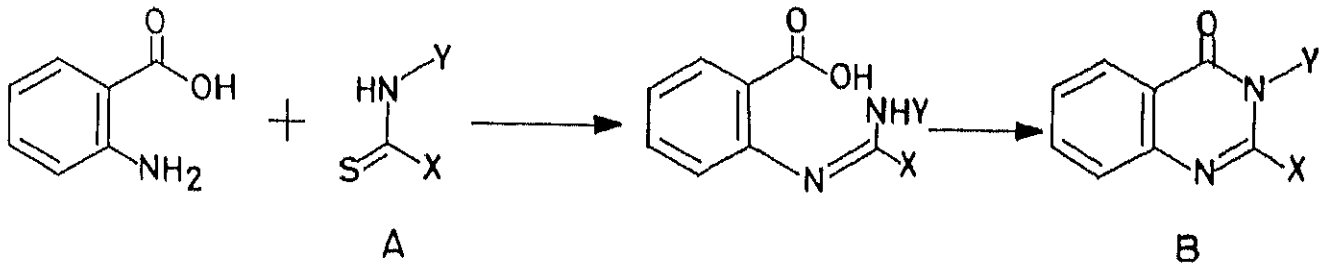
A	B	Ref.
		21
		22
		23
 R = H, Me, Ph, Py, NH_2		24
Ar—$NHCO_2Et$		25

TABLE D

REACTION TYPE



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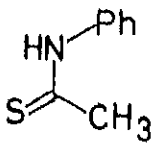
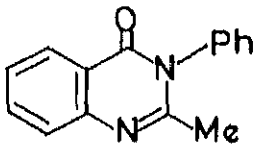
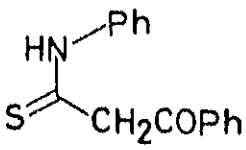
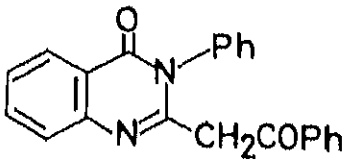
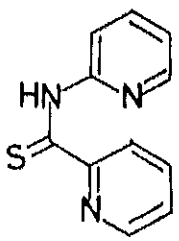
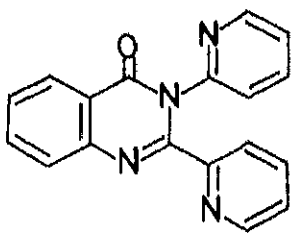
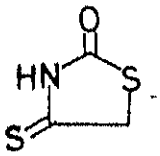
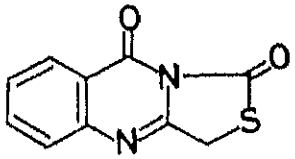
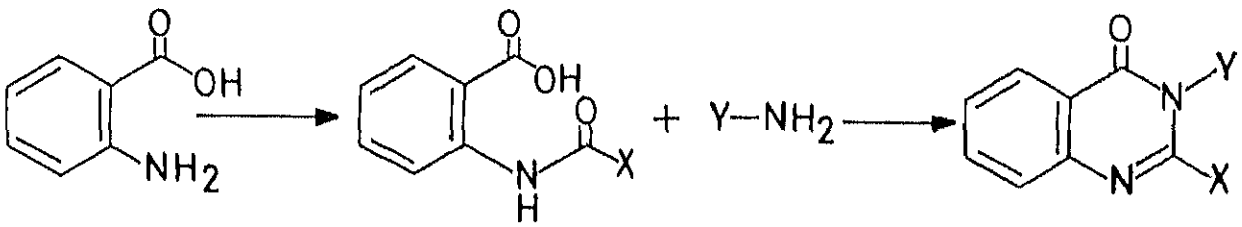
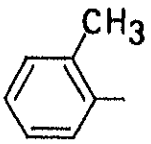
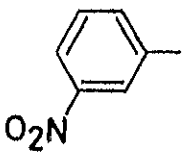
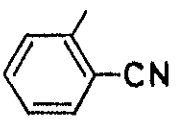
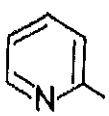
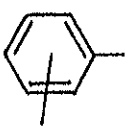
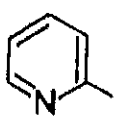
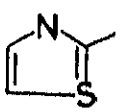
		26
		26
		27
		28

TABLE E

REACTION TYPE



X	Y	Ref.
$-CH_3$	 , Ar	29
$-CH_3$		30
$-CH_3$		31
	 Z (o,m,p) Z = Cl, NO_2	32
Ph	Ph	33
$-CH_2-OPh$		34
$-CH_2OPh$		34

1.3.4 The preparation of quinazolones from I and α-chloro, α-thio, α-thioalkyl and α-alkoxy imines:

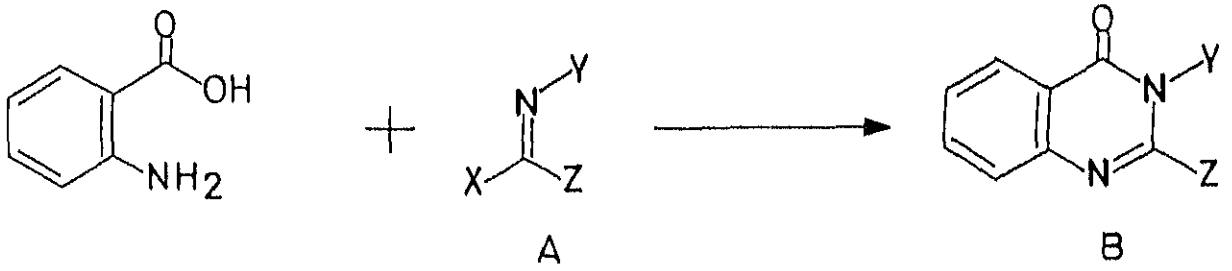
The strategy cited above constitutes one of the most versatile routes to quinazolones and is particularly useful in the construction of polycyclic ring systems in a single operation. Thus, 2-chloro pyrimidines[36], 2-chloro pyridines[37], 3-chloro pyrazines[38], 2-chloro benzothiazones[39], readily react with I resulting in the formation of quinazolones. Several of such systems prepared have therapeutic importance. An interesting illustration of this reaction is the preparation of chiral quinazolones from imino-ether that could be readily prepared from the dipeptide prolyl-glycine[42]. The ease with which this type of reaction takes place is exemplified with the reaction of I and 2-mercapto-oxadiazole leading to the expected quinazolones[43] (TABLE.F).

1.3.5 Quinazoline ring formation involving I and nitriles:

Cyanamide and its derivatives readily react with I leading to 2-amino quinazolines or their derivatives. An interesting reaction of I is the formation of 2-guanyl 4-quinazolones[46], on treatment with dicyanogen in presence of H_2SO_4. This reaction presumably involves the intermediacy of 2-cyano 4-quinazolones. In the case of N-alkylated anthranilic acids which carry a β-carbonyl function, the reaction with either cyanamide or malononitrile leads to quinazolones which

TABLE F

REACTION TYPE



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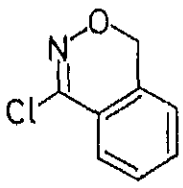
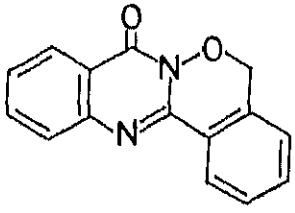
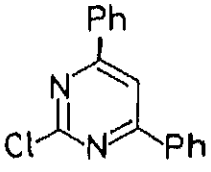
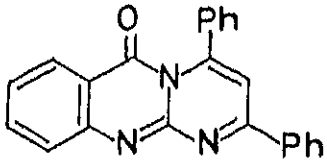
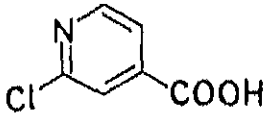
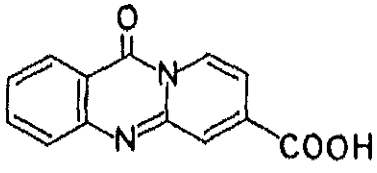
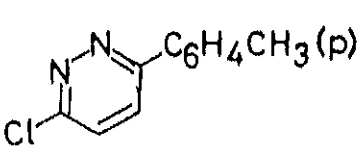
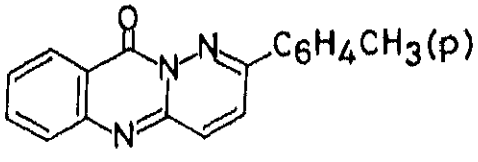
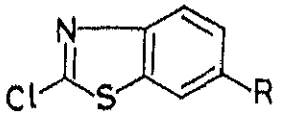
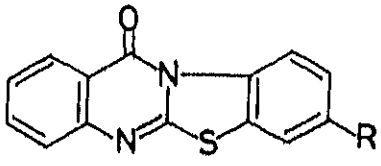
		35
		36
		37
		38
 (R = Cl, NO_2)		39 (contd)

TABLE F

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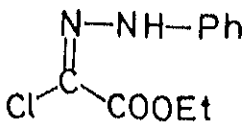
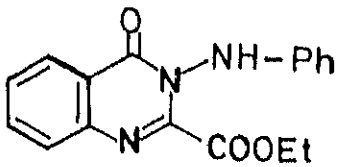
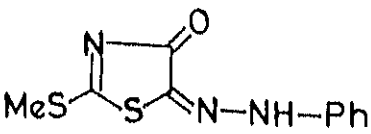
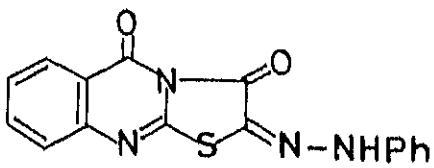
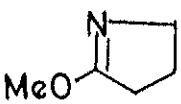
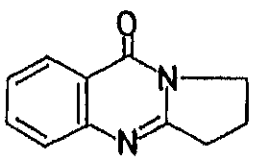
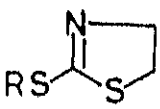
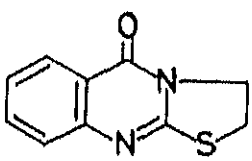
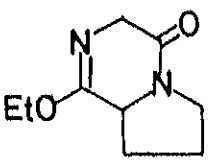
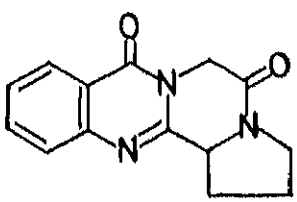
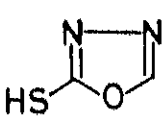
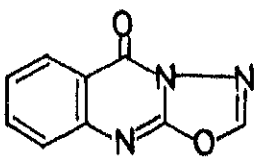
		40
		28
		25
		41
		42
		43

undergo further cyclization to tricyclic heterocycles[47] (TABLE.G).

1.3.6 The synthesis of quinazolones from I and Isothiocyanates and Isocyanates:

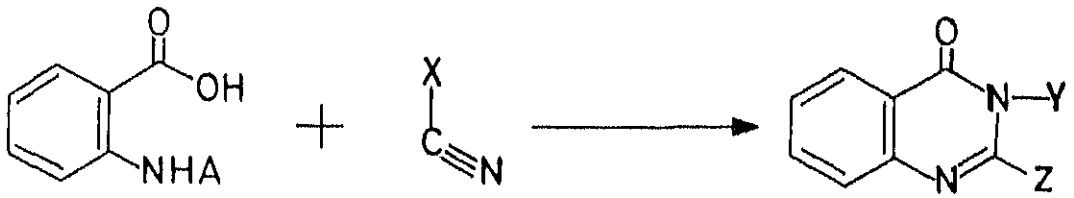
The electrophilic cumulative structural unit present in isothiocyanates and in isocyanates enables the ready formation of 4-quinazolones and is initiated by the nucleophilic amino grouping. Under normal pH conditions, the isothiocyanates give rise to 4-quinazolone 2-thiols; on the other hand isocyanates usually afford, 2,4-dioxoquinazolines. The 2-thiol unit of the product 4-quinazolones (vide supra) enables various transformations. Thus, alkylation of this unit with α-haloacids or their derivatives leads to mesoionic systems[53]. Alternatively this grouping can be replaced by the azide function, by reaction with hydrazine followed by treatment with HNO_2. This compound readily undergoes intramolecular cyclization giving rise to tricyclic tetrazoles[49]. An interesting reaction is the formation of 1,ω-bis 4-quinazolones by reaction with the appropriate isothiocyanates[55] (TABLE.H).

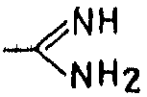
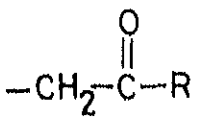
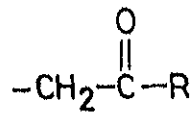
1.3.7 Formation of 4-quinazolones from anthranilic acid methyl ester by reaction with DMF-acetals and amines:

This method enables the preparation of 4-quinazolones in high yields under mild conditions (TABLE.I).

TABLE G

REACTION TYPE



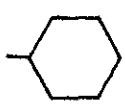
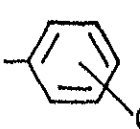
A	X	Y	Z	Ref.
H	$-NH_2$	H	NH_2	44
H	-NHCOPh	COPh	NH_2	45
H	-CN	H		46
	NH_2	H	NH_2	47*
	CH_2CN	H	CH_2CN	47*

* Undergoes further cyclisation

TABLE H

REACTION TYPE

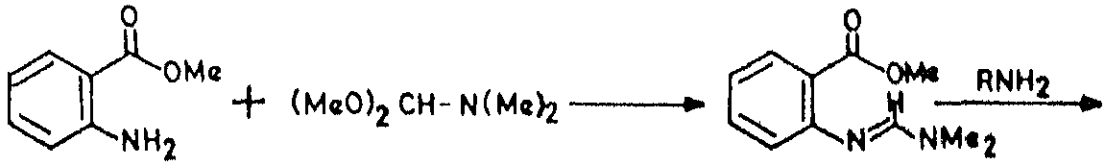
R = H, Me

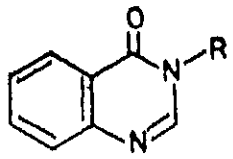
X	Y	Ref.
K	S	48
$-CH_3$	S	49,50
	S	51
C_6H_5	S	52
	S	53,54
$-(CH_2)_n-N=C=S$*	S	55
Bz	S	56,57
R	O	58
	O	59
Ph	O	60,61
$HOOC-CH_2$	O	62

* - The bis-adduct is formed

TABLE I

REACTION TYPE

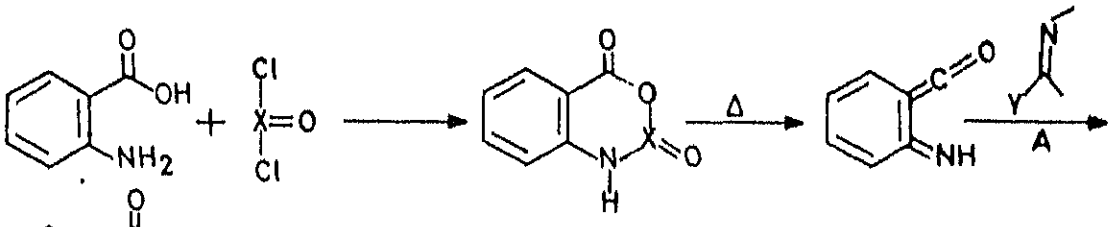


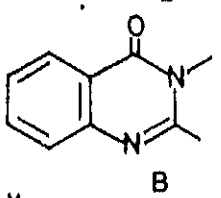


R	Ref.
R = H, NH_2, OH, Ph, $4R'-C_6H_4$ (R' = OMe, Me)	63
Me, C_6H_{11}, $PhCH_2$	

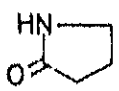
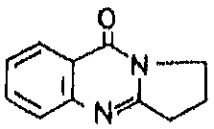
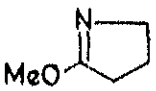
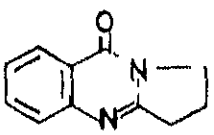
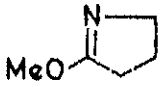
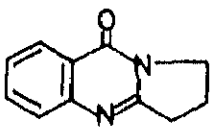
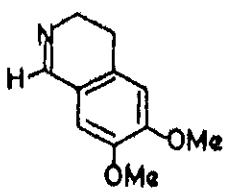
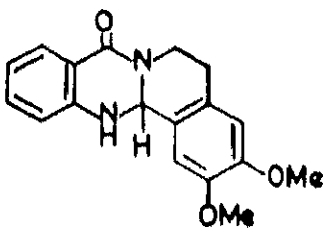
TABLE J

REACTION TYPE





B

X	A	B	Ref.
S			64
S			65
C			65
C			65

1.3.8 Formation of 4-quinazolones from ketene-imine intermediates:

The reaction of I with either $COCl_2$ or $SOCl_2$ leads to cyclic systems which readily undergo extrusion of either CO_2 or SO_2 leading to the generation of highly reactive ketene-imine intermediates. The latter undergo ready reaction with a variety of electron rich π-systems leading to quinazolones. Table.J illustrates the utility of this reaction with particular reference to the formation of polycyclic 4-quinazolones (TABLE.J).

1.3.9 The synthesis of 4-quinazolones from benzoxazones and amines:

The reaction of benzoxazones (1.1) with amines constitutes an excellent procedure for the preparation of a variety of 4-quinazolones (TABLE.K).

1.3.10 Formation of 2,4-dioxoquinazolines from isatoic anhydrides:

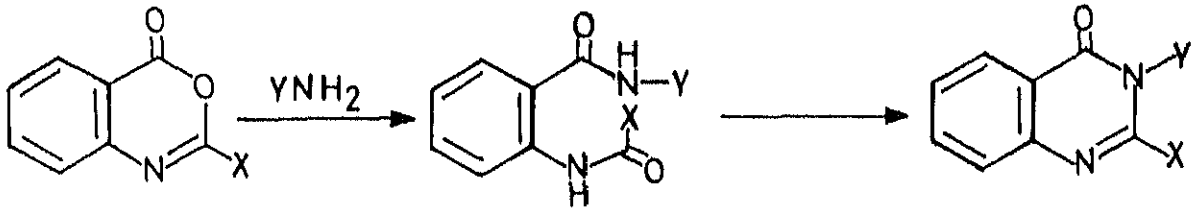
Isatoic anhydrides (1.2) reacts with urea and urethanes giving rise to quinazoline 2,4-diones (TABLE.L).

1.3.11 4-Quinazolones from Isatoic anhydrides:

The reaction of isatoic anhydrides with a variety of amines readily gives the corresponding anthranilic acid amides. These react with either CS_2 or KSCN/HCl giving rise to 4-quinazolones possessing a 2-thiol function[78,80].

TABLE K

REACTION TYPE



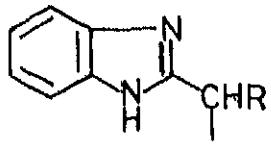
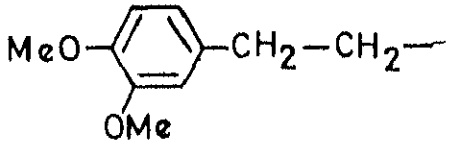
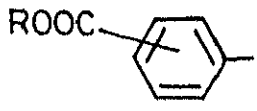
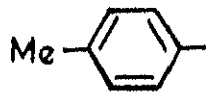
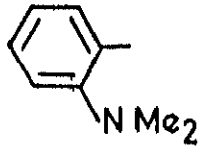
X	Y	Ref.
Me, Ph, CH_2Ph	Ph	66
Ph		67
CH_3		68
CH_3		69
$PhCONHCH_2-$ $-CH=CH-C_6H_5$ $-CH(OH)C_6H_5$	OH	70
Me		71
Ph		71
CH_3	Me, Bu	72, 73
$-CH_2-CH_2COOMe$	Me, Bu	74

TABLE K

REACTION TYPE (contd)

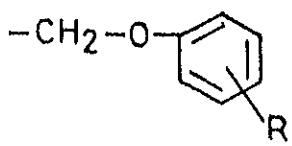
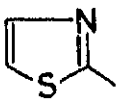
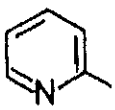
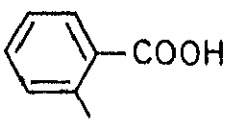
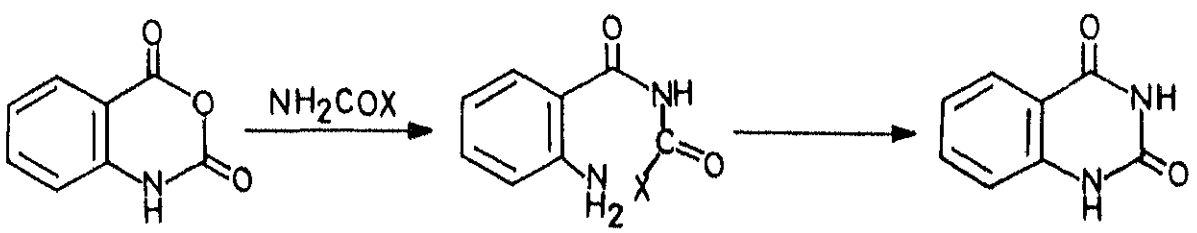
X	Y	Ref
		75
R = o - Me o - Cl p - NO_2		75
Me , Et , $CHMe_2$		76

TABLE L

REACTION TYPE



X	Ref.
NH_2 , OEt	77

On the other hand such intermediates on treatment with either $COCl_2$ or $ClCO_2Et$ gives 2,4-dioxo quinazolines[79]. Finally, 4-quinazolones could be directly obtained from isatoic anhydrides by reaction with amines and ortho-formates[77] (TABLE.M).

2. RING FORMING REACTIONS OF ANTHRANILAMIDE (II):

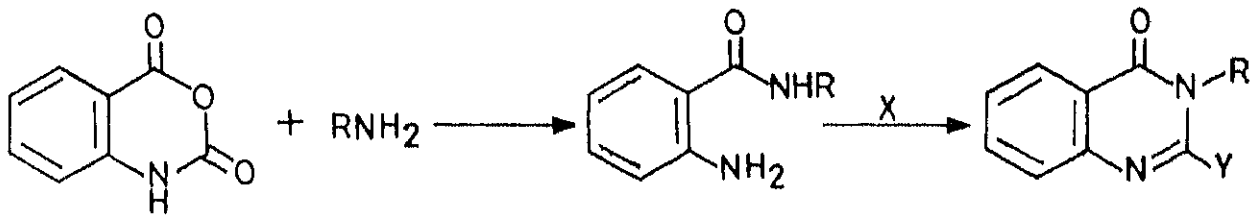
2.1.1 Quinazolones by reaction with carboxylic acid or their equivalents:

Most of the quinazolone syntheses described above use anthranilic acid (I) as the starting material and in rare cases the corresponding ester. Anthranilamides are intermediates in the synthesis of quinazolones (TABLE.C,K, L,M). This section relates to quinazolone syntheses starting with anthranilamide.

The two amino ends of II readily interact with formic acid or its derivatives or its equivalents leading to a variety of 4-quinazolones. An interesting reaction of this type is the formation of either linear or angular tricyclic quinazolones by reaction of II with either butyrolactone or valerolactone. TABLE.N illustrates the range of quinazolones that could be prepared by this strategy (TABLE.N).

TABLE M

REACTION TYPE



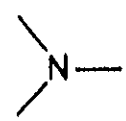
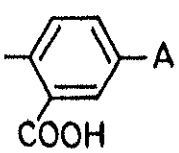
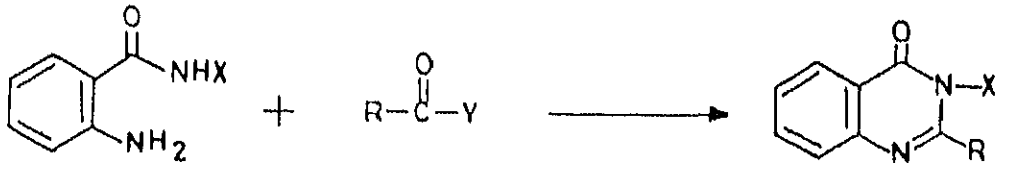
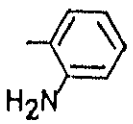
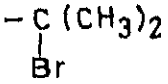
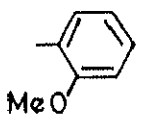
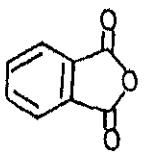
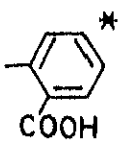
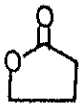
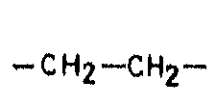
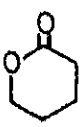
R	X	Y	Ref.
Ph	$HC(OEt)_3$	H	77
Ph-NH	CS_2	SH	78
Ph-NH	KSCN / HCl	SH	78
—NHAc	CS_2	SH	78
	$COCl_2 / ClCO_2Et$	OH	79
	CS_2	SH	80

TABLE N

REACTION TYPE



X	Y	R	Ref
R′	Cl	OEt	81
Ph	OH	H	82,83
NH_2	OAc	CH_3	84
Ph	OAc	CH_3	84
H	OH/PhO/NH_2	$-CH_2CN$	85
R′	OH	Ar	86
H	OH	$-CH_2Ph$	87
H	OH		87
H	Br		88
H	Cl		89,90
H	NH_2	Alkyl/aryl	91
H	OAc	CH_3	92
H			93
H			94,95
H		$-(CH_2)_4-OH$*	95
H	$HC(OEt)_3$	H	96

*- undergoes further cyclization

2.1.2 Preparation of 4-quinazolones and 1,2-dihydro 4-quinazolones by reaction of II with carbonyl compounds:

An interesting reaction of II is the formation of aminals on treatment with various carbonyl compounds. In the case of aldehydes, the resulting adduct could be readily oxidized by a variety of agents including $KMnO_4$ and nitrobenzene leading to 4-quinazolones[97-100]. In the case of 1,3-dicarbonyl compounds, the primary adduct undergoes retro-aldol type reaction leading to 4-quinazolones functionalised at the 2-position[103,104]. An interesting reaction is the efficient transformation of, to 4-quinazolone with the formic acid transfer agent α-cyano β-ethoxy acrylic ester[105] (TABLE.O).

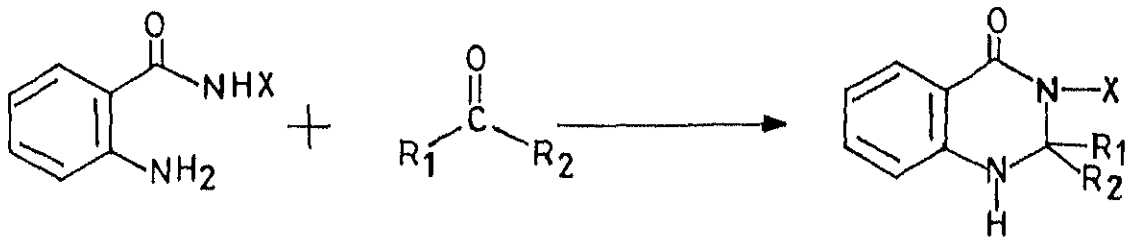
3. RING FORMING REACTIONS OF ANTHRANILONITRILE (o-CYANO ANILINE, III):

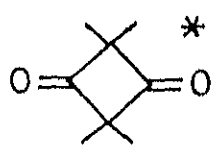
3.1.1 The preparation of 4-amino quinazolines by reaction of III with nitriles:

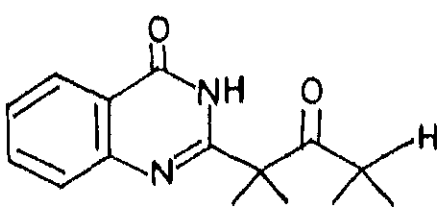
The reaction of III with a variety of nitriles gives 2-substituted 4-amino quinazolines. The reaction is particularly facilitated with N-cyano compounds. The resulting 2-nitrogen functionalised 4-amino quinazolines could be readily transformed to 2-substituted quinazolines by reaction with organometallic compounds[107,109]. In the case of appropriately N-substituted o-cyano anilines, this reaction

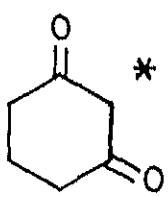
TABLE O

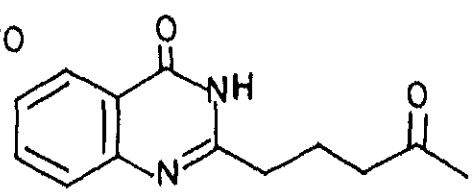
REACTION TYPE

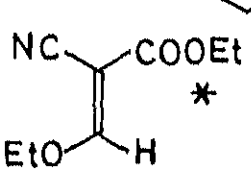


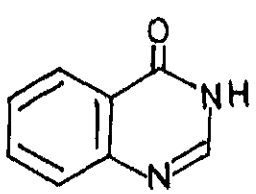
X	R_1	R_2	Ref
Ar	H	H	97
H	Ar	H	98,99,100,101
H	Ph	Bz	102
H		–	103

* - Product is 

H			104

* - Product is 

H			105

* - Product is  + $H_2C(CN)CO_2Et$

leads to tricyclic heterocycles resulting from further cyclization of the initially formed 4-amino quinazolines[47] (TABLE.P).

3.1.2 4-Amino quinazolines by reaction of N-acyl o-cyano anilines with amines:

The above reaction is promoted by P_2O_5, presumably to generate the required electrophilic intermediate from the acylamino function. The procedure is useful for the preparation of a variety of 2-substituted 4-amino quinazolines. An interesting aspect is the facile Dimroth rearrangement of the initially formed 3N-substituted quinazolium systems[110]. An interesting variant of this is the reaction of o-cyano aniline with ethyl orthoformate followed by reaction with alkyl amines. In this case the imine ether that is formed initially readily undergoes further reaction including Dimroth rearrangement[111] (TABLE.Q).

3.1.3 4-Amino quinazolines from III and imino ether hydrochlorides:

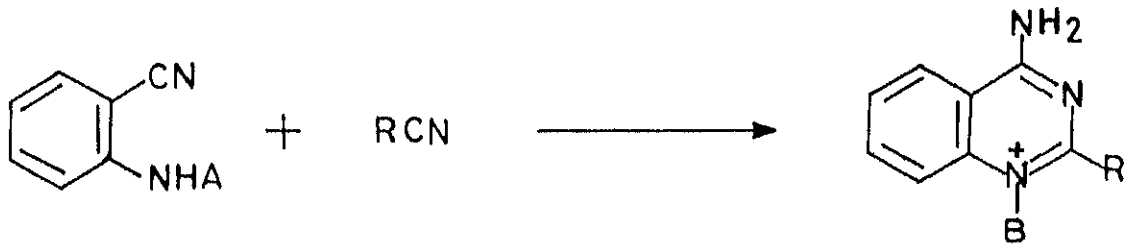
Imino ether hydrochlorides — available from the reaction of the —CN function with EtOH.HCl — react with o-cyano aniline to produce 4-aminoquinazolines[112] (TABLE.R).

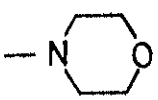
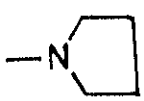
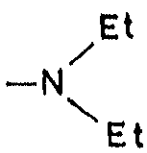
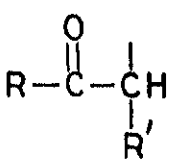
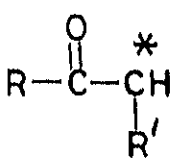
3.1.4 The preparation of 4-amino quinazolines by reaction of III with isocyanates or isothiocyanates:

The reaction involved here is similar to that pertaining to the formation of 4-quinazolone from I (TABLE.H).

TABLE P

REACTION TYPE

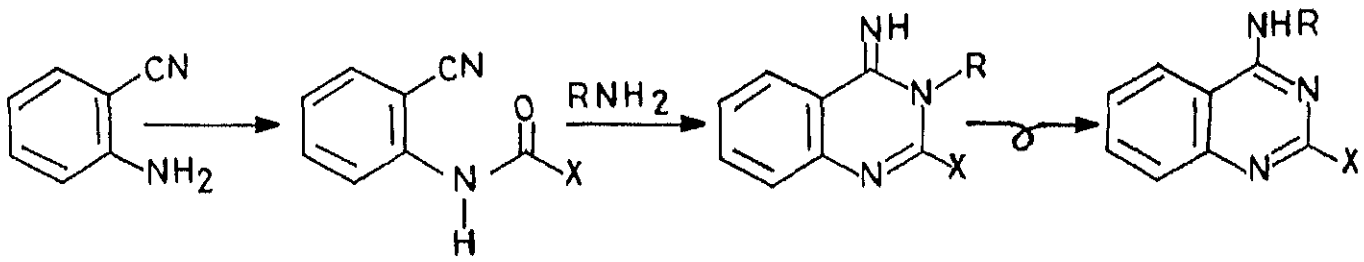


A	R	B	Ref
H		–	106
H		–	107
H	Me , Et	–	108
H		–	109
	NH_2		47

* - The product undergoes cyclization

TABLE Q

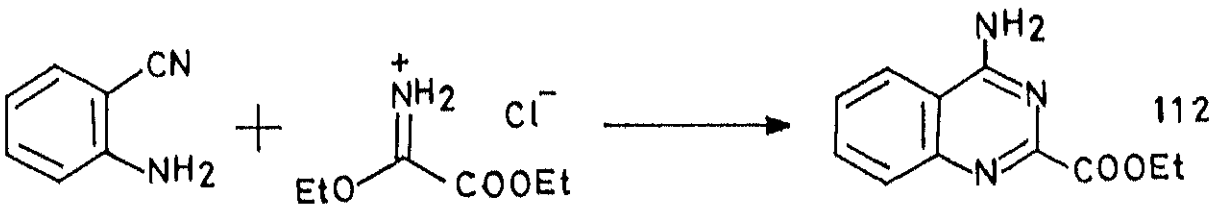
REACTION TYPE



X	R	Ref
Me, t-Bu, Ph	Me, Pr, EtCHMe, Ph	110
H (as imino ether)	CH_3	111

TABLE R

REACTION TYPE



112

The reaction of III with isocyanates and isothiocyanates is of additional interest because of the presence of the 4-amino functional unit which could be advantageously used for the preparation of additional heterocyclic systems[115,116,117] (TABLE S)

4. RING FORMING REACTIONS OF 5-AMINO IMIDAZOLE 4-CARBOXAMIDE (IV).

4.1 THE PREPARATION OF HYPOXANTHINES AND ADENINES FROM IV:

The compound IV is a very important intermediate in biological systems. The terminal $-NH_2$ functions present in IV could be linked with a single carbon unit giving rise to hypoxanthines and adenines. They could also be linked through nitrogen by a simple diazonium coupling reaction[123] (TABLE.T).

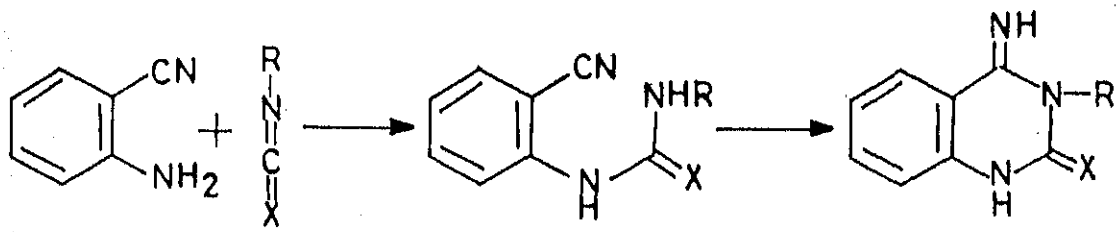
5. RING FORMING REACTIONS OF 4-CYANO 5-AMINO IMIDAZOLE (V):

5.1 THE FORMATION OF PURINE AND PURINE ANALOGUES FROM V:

4-Cyano 5-amino imidazole (V) is an excellent precursor for the preparation of a variety of purines of great current interest. Direct nucleoside formation is possible by reaction of V and appropriately protected sugars through either the imino ether function or the imino thio ether function at the code position[128,129]. An interesting reaction of V is the formation of a thia adenine analogue

TABLE S

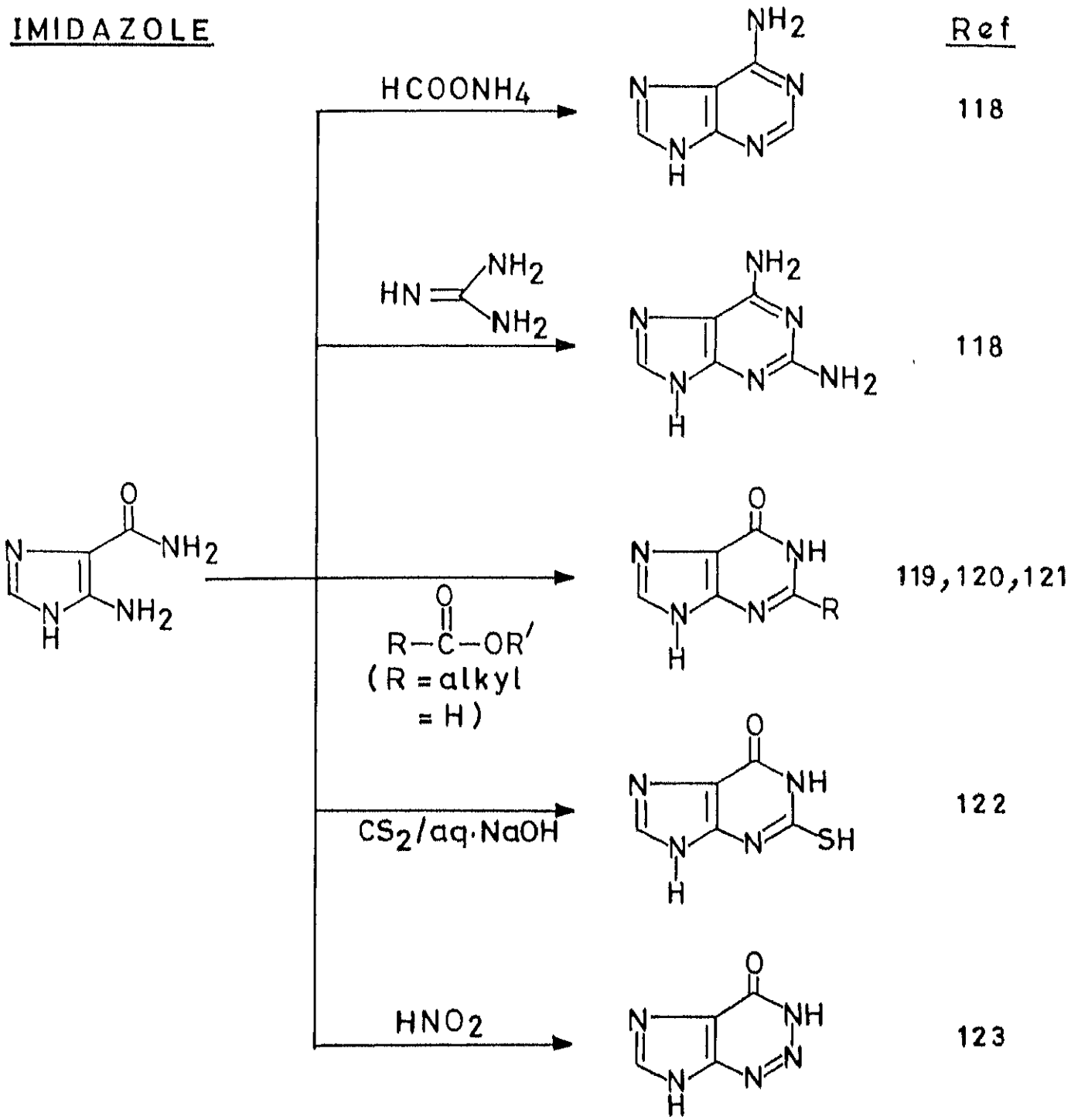
REACTION TYPE



R	X	Ref
R	S	113
Ph	S	114
$CH_2-CH=CH_2$	S	115
$Cl-CH_2-CH_2$	O*	116
$EtOOC-CH_2$	O*	117

*- Cyclic intermediate undergoes cyclization

TABLE I


IMIDAZOLE
Ref
HCOONH4
118
HN=C(NH2)NH2
118
R–C(=O)–OR′
(R = alkyl
= H)
119,120,121
CS2/aq.NaOH
122
HNO2
123

with CS_2[126] The reactions with V are summarised in TABLE.U.

The ene-aminoacid grouping affixed to benzene and imidazole has provided methodologies for a wide selection of heterocyclic systems (vide supra). In sharp contrast, a detailed search of the literature shows that the chemistry of this grouping attached to other ring systems have hardly merited examination. It must be obvious that such systems could provide facile routes to various kinds of heterocyclic rings. The handful examples that are reported and which belong to other categories are described below.

6. RING FORMING REACTIONS OF 2-AMINOTHIOPHENES HAVING A CARBOXYL OR AN EQUIVALENT GROUPING AT 3-POSITION (VI):

2-Aminothiophenes having a carboxyl or equivalent function at the 3-position readily undergo ring forming reactions very similar to that described with the benzenoid and imidazole systems (TABLE.V).

7. THE REACTIONS OF FURANS AND DIHYDROFURANS POSSESSING THE 1,2-ENE AMINO ACID FUNCTION:

In sharp contrast to the thiophene system described above, either the furanoid or the dihydrofuranoid units possessing the 1,2-ene-amino acid function exhibit a strong tendency for rupture of the parent ring that generally takes

TABLE U

O-Cyano-amino Imidazole

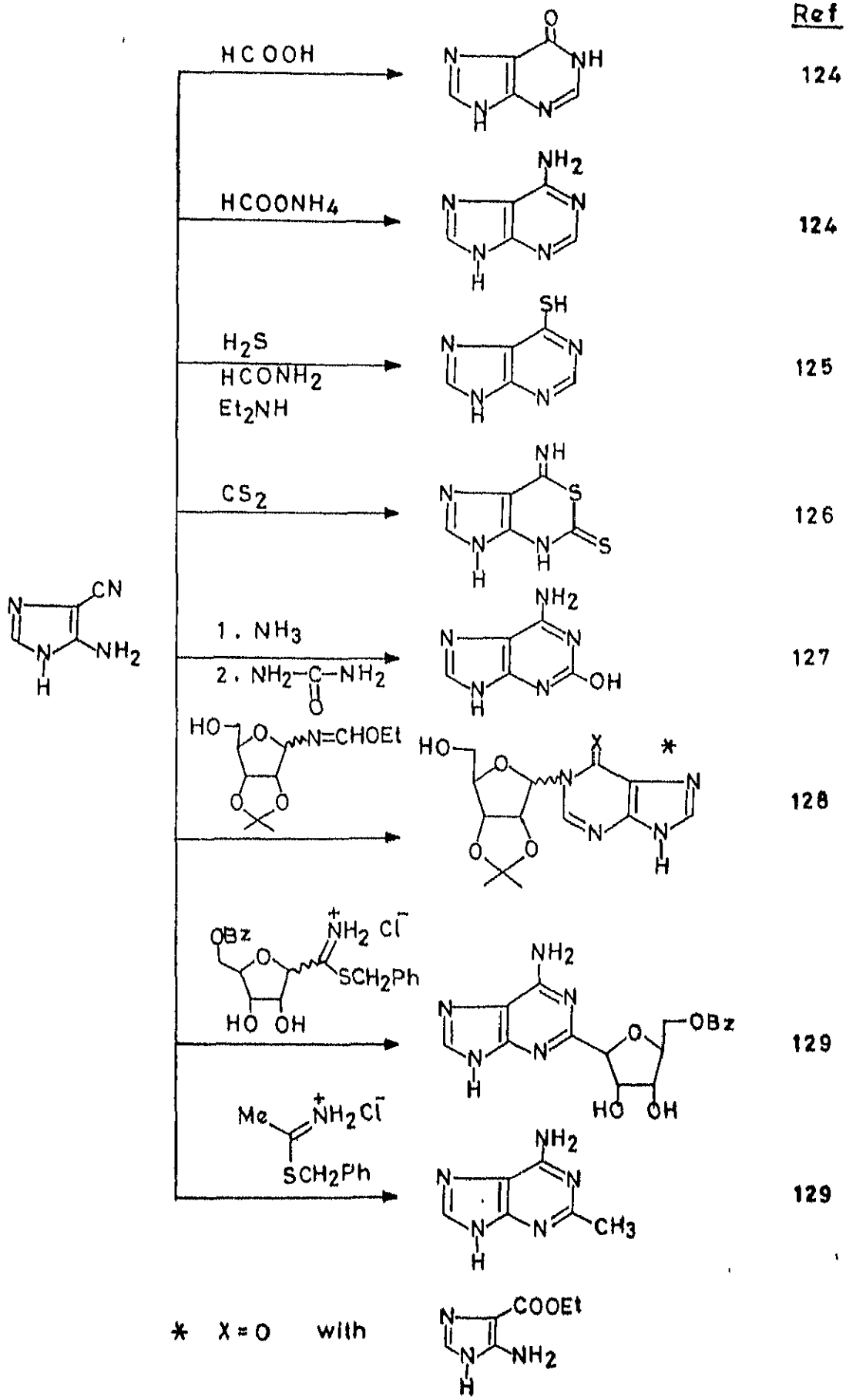


TABLE V

Ref

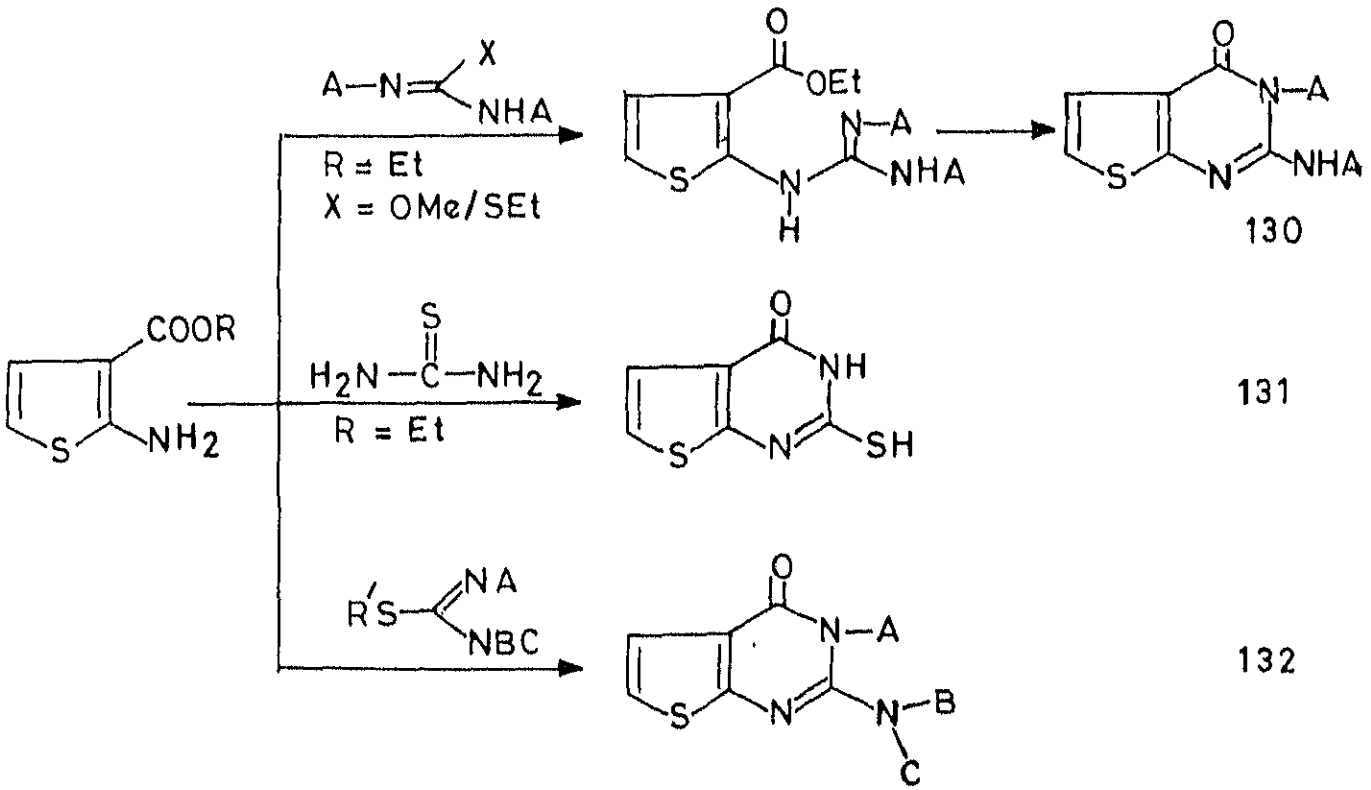
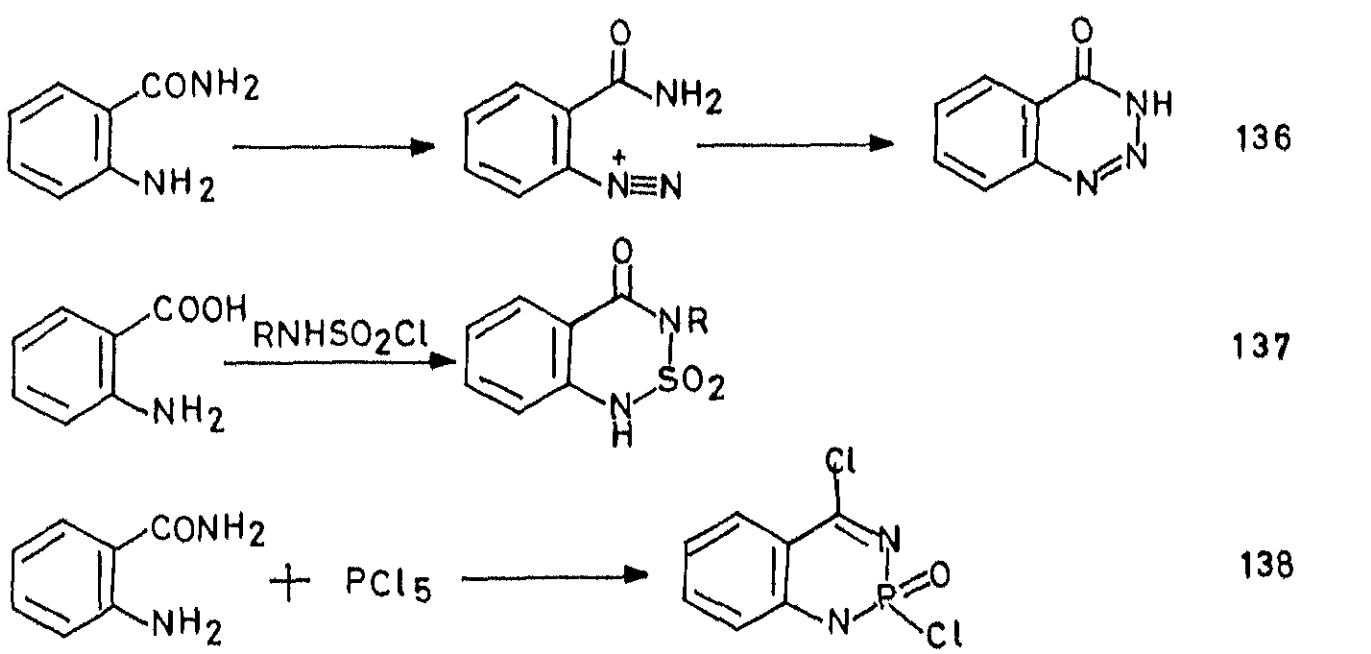


TABLE X



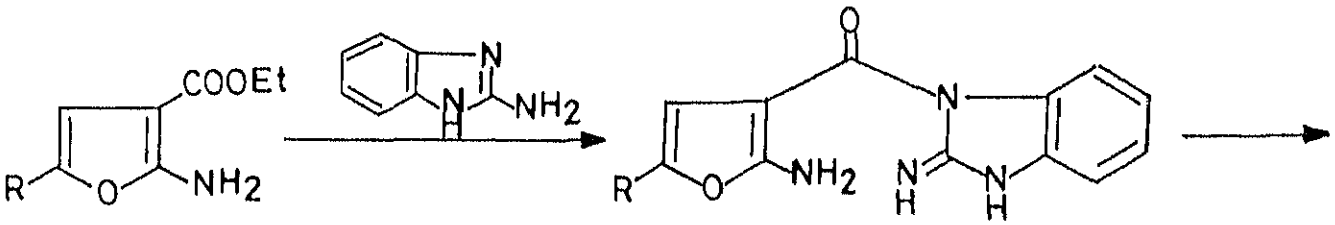
place concomitant with the cyclization. Thus the reaction of 2-amino 3-carboethoxy furans with 2-aminobenzimidazole leads to tricyclic systems at the expense of the rupture of the furan ring[134]. Similar reactions are encountered with the corresponding 4,5-dihydrofurans with amidines and hydrazines[135] (TABLE.W).

8. THE 1,2-ENE-AMINO ACID UNIT AS A PRECURSOR TO UNUSUAL QUINAZOLINE ANALOGUES.

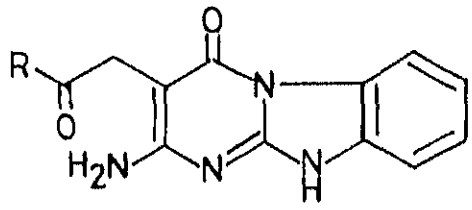
This reaction type is exemplified with the formation of 2-aza 4-quinazolone[136], 2-sulphonyl[137] analog of 4-quinazolone and an unusual phosphorous heterocycle[138] (TABLE.X).

As stated previously, the chemistry of 1,2-ene-amino acid systems were analyzed as appropriate background for the present work (SECTION C), which, inter alia, brings out the property of such compounds as parents for the template synthesis of a variety of heterocycles. The potential of the compounds cited above as medium for template synthesis has been examined and presented at the end of the next section.

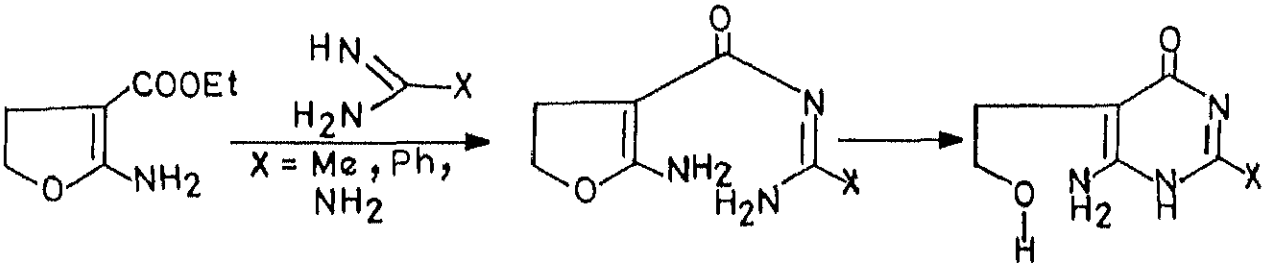
TABLE W

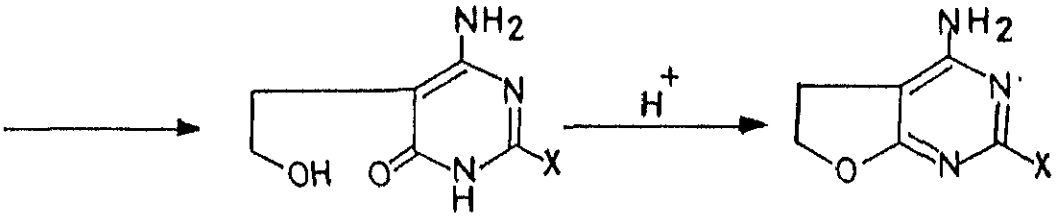


Ref



134





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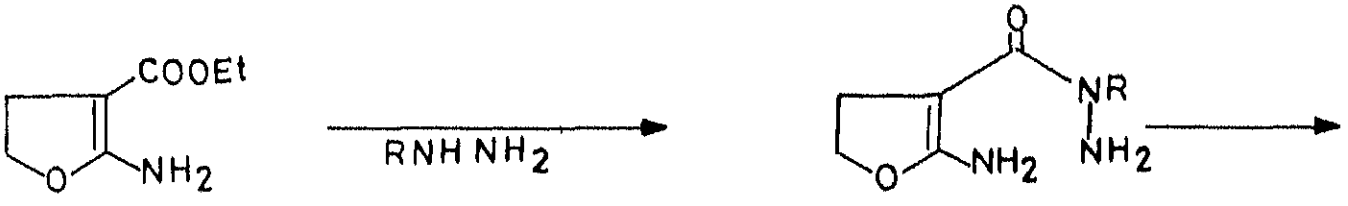

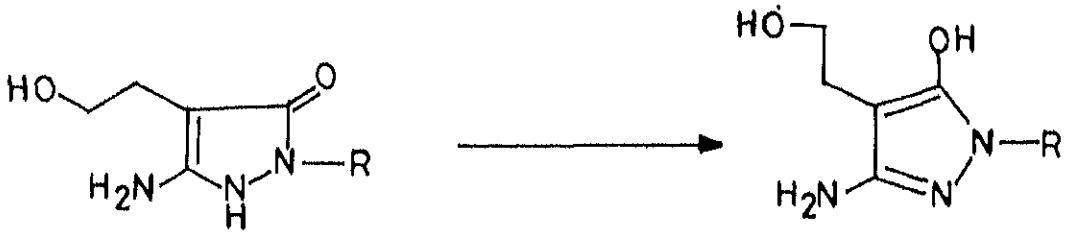

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The present survey complements, supplements and updates information cited above.

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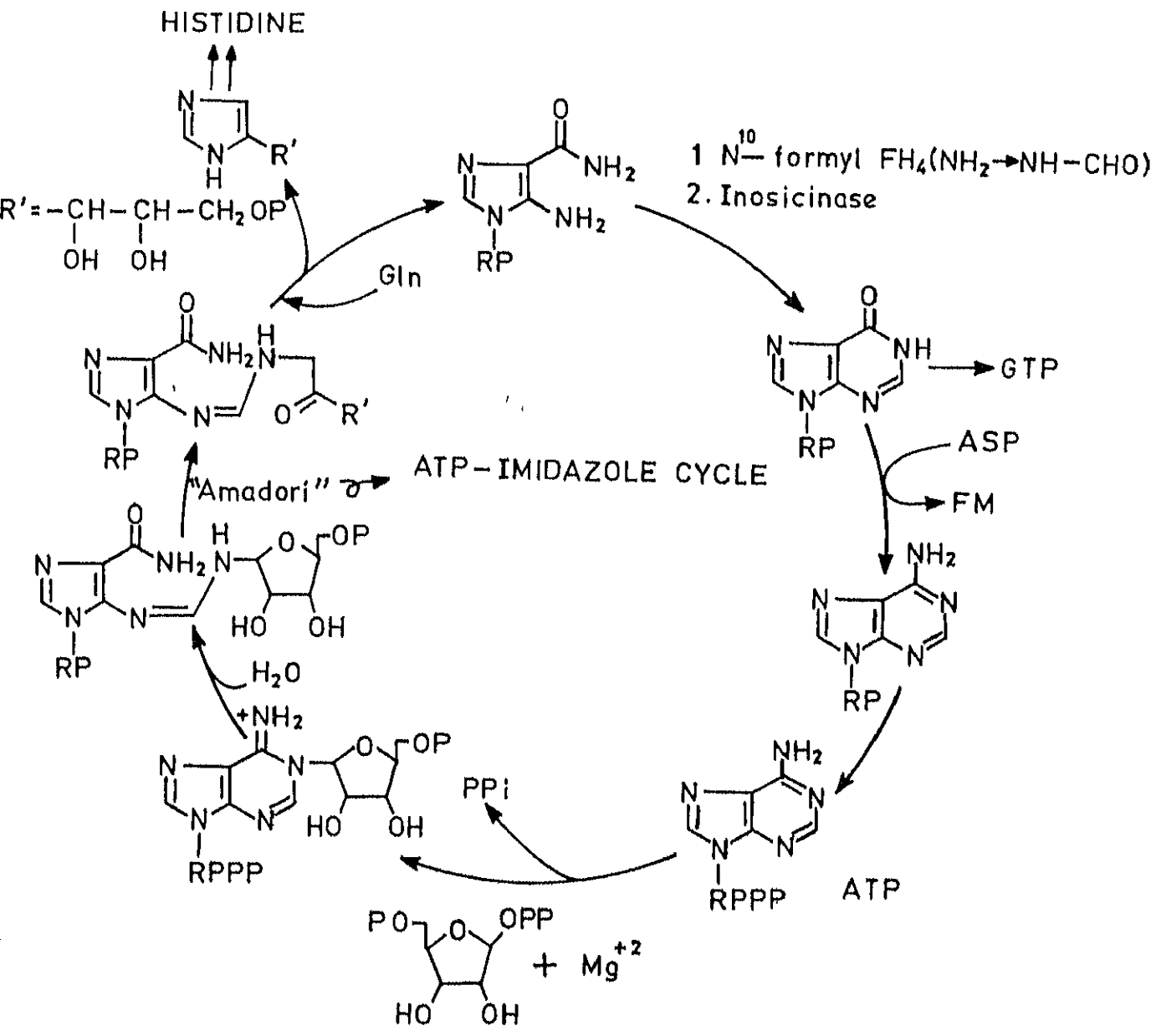
I.C. PRESENT WORK

An attractive facet of the art in organic synthesis would be the creation of structures on a template[1] which can be re-cycled. Such a strategy - although used by Nature for the biosynthesis of compounds vitally associated with life processes[2] - has been neither exploited nor systematically explored thus far. A unique example of template strategy in Nature is the ATP-Imidazole cycle wherein a daughter imidazole is grown on a mobile parent imidazole *via* a cyclic pathway that is linked to the biosynthesis of the purine code bases ATP and GTP as well as to the imidazole amino acid histidine[3]. The cycle is initiated by the parent, namely, protected 5-amino imidazole-4-carboxamide by acceptance of elements of formic acid to give 9-protected hypoxanthine. This is aminated to adenine and then to, *via* sequence, specific 1N- incorporation of ribose phosphate, hydrolysis, Amadori rearrangement, enamination, cyclization and cleavage to the daughter 5-substituted imidazole and the parent imidazole template that now can initiate another cycle. The daughter product is subsequently tooled down to histidine. Details of the cycle, arrived at as a result of extensive experimentation[3a-c], are presented in (CHART I.C.1).

CHART I.C. 1



The methodologies of growing the daughter on the parent (CHART I.C.1), can be analyzed in terms of the stepwise introduction of the needed 1-nitrogen and 3-carbons with the amide nitrogen of the parent destined to be part of the daughter imidazole. The protocol involves the introduction of the carbon bridge that connects the two nitrogen functionalities of the parent, specific 1N-alkylation leading to -CH=C(a)-NH(b) attachment and processes associated with the formation and separation of the daughter product (CHART I.C.2).

The chemical simulation of the ATP-Imidazole cycle was initially carried out on a model which possessed the operating part of the cycle, namely, the vicinal disposition of the $-NH_2$ and $-CONH_2$ units and substituting the more reactive imidazole moiety with a phenyl ring. Thus, all early experiments made use of anthranilamide rather than the N-substituted-5-aminoimidazole 4-carboxamide as the template.

Anthranilamide (2) was readily converted to 3,4-dihydro-4-quinazolone (4) by treatment with dimethylacetal of DMF and then to an array of 3N- substituted 4-quinazolones. All endeavours to rupture these specifically at the 4-oxo location, that would lead to the release of the -COOH function and which is the pathway that is established for the ATP-Imidazole cycle (CHART I.C.1, CHART I.C.2 , Path A) did not succeed, but gave, frequently, products arising from

re-arrangement. The studies relating to this aspect are presented in the Part-II of the thesis. Thus, it became necessary to modify Nature's strategy and this was endeavoured *via* prior cyclization of the specifically 3N- substituted-4-quinazolones to tricyclic systems that have capability to undergo further rupture to daughter products (CHART I.C.2, Path B). Here again, several attempts to bring about the cyclization using conjugate bases generated *in situ* at the terminii of the 3N- substituted-4-quinazolones did not succeed due to incursion of undesirable 2-3 bond rupture. These experiments, in several cases, demonstrated that the anticipated tricyclic systems were formed. However, they existed in equilibrium with the open precursors. The further course of the reactions here was dictated by the propensity of these to undergo 2,3-bond rupture, often as a result of addition of nucleophiles to the 1,2-bond.

A closer examination of the course of the established pathway involved in the ATP-Imidazole cycle (CHART I.C.1) revealed that the cyclization leads to a product that would rupture to give an aromatic derived product. Consequently, it was surmised that the cyclic intermediate arising from addition to the 1,2-bond of quinazoline (Path B; CHART I.C.2) could be induced to undergo the desired 3,4-bond rupture, in the event this process could be assisted by the formation of aromatic daughter products. This proved to be the case.

CHART I.C.2

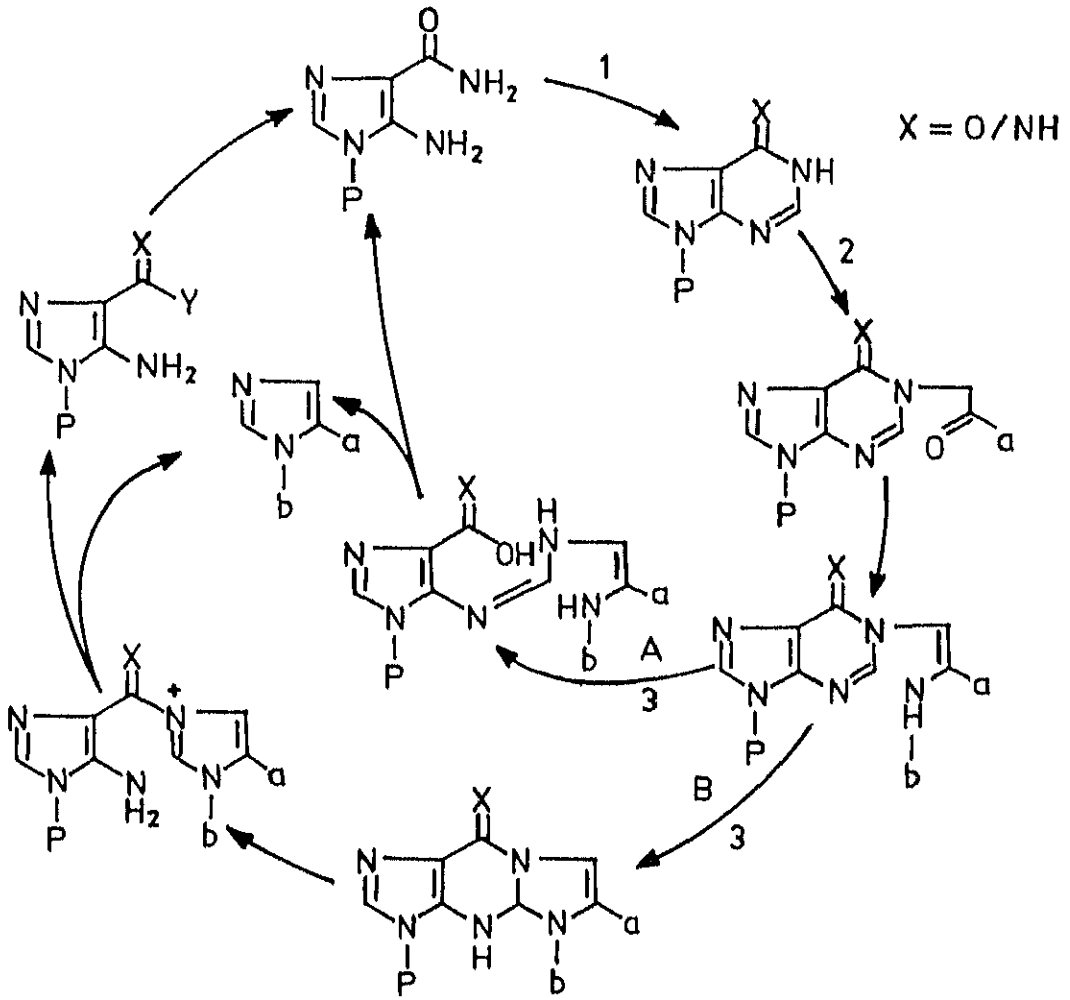
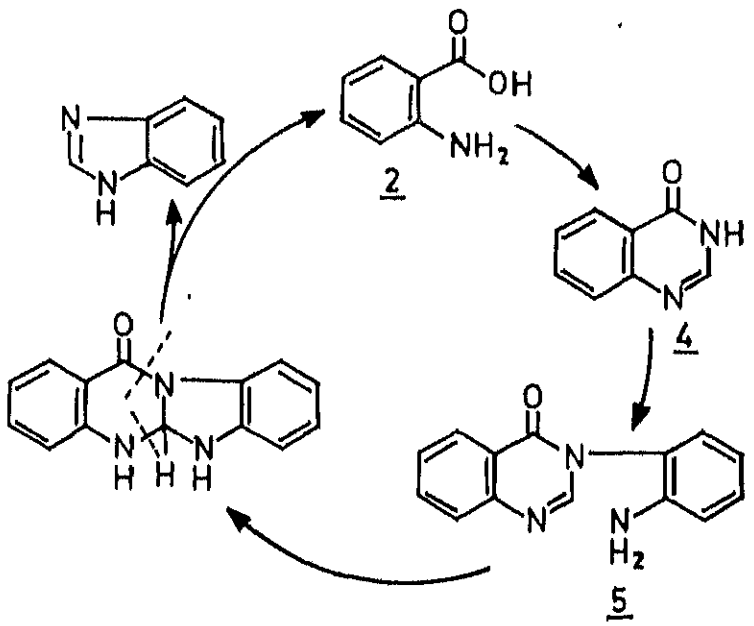


CHART I.C.3



The reaction of 4-quinazolone (4) with o-phenylenediamine gave in 10% yields the 3N-substituted compound 5, that has capability to undergo cyclization to the 1,2-bond followed by rupture leading to aromatic daughter products. The reaction of 5 with aqueous alkali gave in 73% yields the derived product benzimidazole and the template anthranilic acid (79%), thus demonstrating that the expected course of events indeed took place (CHART I.C.3).

The pathways leading to benzimidazole and anthranilic acid in the above experiment from 5 are precisely that envisaged in CHART I.C.2, Path B. Thus, it appears that the generation of an open enamine unit such as that present in 5 is essential to bring about the desired template directed reaction. Such an approach provided a satisfactory solution to the problem, initially with the formation of imidazole from anthranilamide template and culminating in the creation of an imidazole from an imidazole parent.

The strategy that led to the successful demonstration of anthranilamide (2) as a template for imidazole synthesis proceeded through the sequence, transformation to 4-quinazolone (4), specific alkylation at the 3-location with either phenacyl bromide or bromoacetone, reaction with a primary amine leading to the formation of the daughter imidazole and the modified parent, which could be transformed to 2, to

start another cycle (CHART I.C.4).

4-Quinazolone (4) which was extensively used in the present work, was prepared either from anthranilamide (2) and DMF-acetal[4] or, more conveniently, from anthranilic acid and formamide[5].

Specific 3N- alkylation of 4-quinazolone (4) was achieved by treatment of its conjugate base-generated with 1 equivalent of KOH-with phenacyl bromide in ethanol to give in 40% yields 3-phenacyl-4-quinazolone (6) mp 159°C[6]. By a similar procedure 3-acetonyl-4-quinazolone (7), mp 158°C was prepared using bromoacetone in 50% yields.

2: mp : 108°C

ir : ν_{max}(KBr) cm^{-1}: 3440, 3060 (br, NH_2), 1710 (amide carbonyl)

4: mp : 216°C

ir : ν_{max}(KBr) cm^{-1} : 3200, 3170 (amide NH), 1700 (amidecarbonyl)

5: mp : 140°C

ir : ν_{max}(KBr) cm^{-1}: 3300-2800 (br,NH), 1690 (amide carbonyl), 1615, 1565 (C=C, C=N)

m/z : 146, 118, 91

6: mp : 159°C

ir : ν_{max}(KBr) cm^{-1} : 1690 (-CO), 1665 (amide carbonyl)

nmr : $\delta(CDCl_3)$, 60 MHz : 5 45 (s, 2H, $-C\underline{H}_2$), 7 35-8.45 (m, 10H, aromatic)

m/z : 264 (M^+), 159 (M^+ - PhCO)

7: mp . 158°C

ir : ν_{max}(KBr) cm^{-1} : 1720 (-CO), 1675 (amide carbonyl)

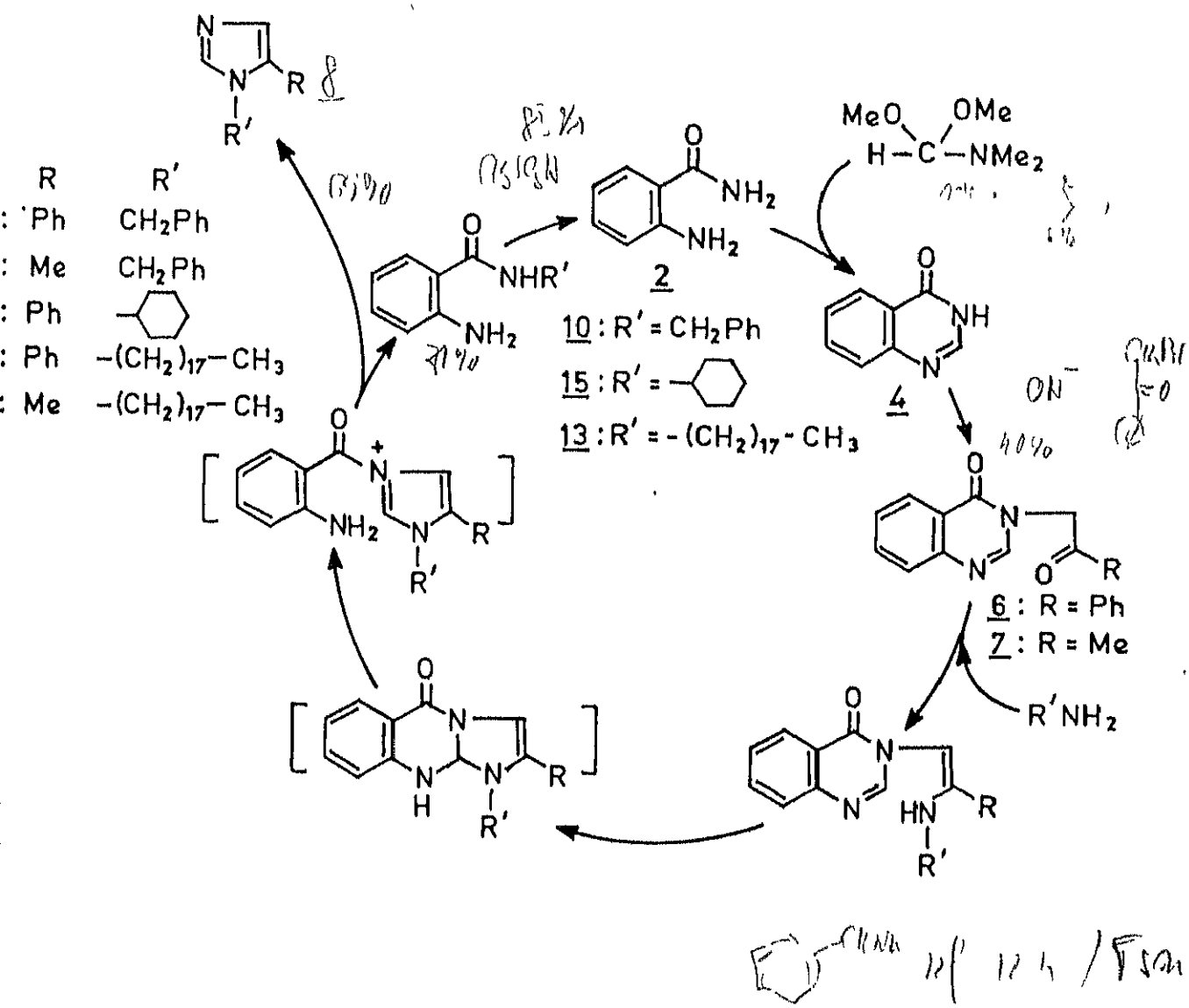
nmr : $\delta(CDCl_3)$, 60 MHz :2.35 (s, 3H, $-COC\underline{H}_3$), 4.85 (s, 2H, $-C\underline{H}_2$), 7.3-8.4 (m, 5H, aromatic)

m/z : 202 (M^+), 159 (M^+ - $COCH_3$).

At the outset, compound 6 was reacted with benzylamine and p-TsOH to generate the enamine intermediate. In the event, fortunately, the reaction proceeded further, to yield the derived imidazole. Subsequently, the optimum conditions with reference to the amine employed, the p-TsOH needed, and the duration of the reaction was worked out in each case. The reaction could be readily monitored by tlc in terms of the disappearance of the starting materials and the formation of the derived product as well as the modified parent.

Thus, compound 6 proceeded through the cycle (CHART I.C.4) on reflux for 12 hours with benzylamine

CHART I.C.4


R R'
Ph CH2Ph
Me CH2Ph
Ph
Ph -(CH2)17-CH3
Me -(CH2)17-CH3
2
10 : R' = CH2Ph
15 : R' =
13 : R' = -(CH2)17-CH3
4
6 : R = Ph
7 : R = Me
R'NH2
MeO OMe
H-C-NMe2

(4 equivalents) and p-TsOH (2 equivalents), leading to the template product, 1-benzyl 5-phenyl imidazole 8, in 69% yields and the modified parent anthranilbenzylamide 10 in 71% yields. The structural assignment for imidazole 8 is fully supported by spectral and analytical data and by comparison with an authentic sample.

8: mp : 111°C

nmr . $\delta(CDCl_3)$, 60 MHz : 5.1 (s, 1H, $-C\underline{H}_2-Ph$), 6.7-7.9 (m, 12H, aromatic)

m/z : 234 (M^+)

10: mp : 123°C

ir . ν_{max} (KBr) cm^{-1}: 3480 (NH_2), 3310 (NH) 1630 (-amidecarbonyl)

nmr : $\delta(CDCl_3)$, 60 MHz : 4.55 (d, 2H, $-C\underline{H}_2-Ph$), 5.25 (br, 2H, $N\underline{H}_2$), 6.7-7.5 (m, 10H, aromatic).

The sequence of events starting from the parent anthranilamide 2 leading to the derived imidazole 8 and the modified parent 10 are presented in CHART I.C.4. The direct transformation of 6 to 8 and 10 are envisaged as taking

place via, the steps, enamine formation, cyclization to tricyclic intermediate, which is cleaved readily to a reactive acylated imidazole that rapidly undergoes transformation to 8 and 10 with benzylamine. This rationalization is supported by various observations. The alternative mode of reaction of benzylamine with 6 would be either addition to the 4-oxo grouping resulting in the opening of the 3,4-bond, or addition to the 1,2-bond of quinazolone followed by rupture of the 2,3-bond. That these events do not take place under the conditions of the 6 → 8 + 10 change is demonstrated clearly by studies on 3-methyl 4-quinazolone (35), a compound which has possibilities for the two alternate modes discussed above, but whose ligand lacks the capability for enamine formation.

Compound 35 was prepared by alkylation of 4-quinazolone (4) with MeI.

35: mp : 95-96°C

ir : ν_{max} (KBr) cm^{-1} : 1665 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz : 3.59 (s, 3H, $-CH_3$), 7.2-8.4 (m, 5H, aromatic).

In the event, the reaction of 35 with benzylamine and p-TsOH in refluxing xylene under condition of the 6 → 8 + 10 change led to the total recovery of the starting material, thus strongly supporting the sequence of events envisaged in CHART I.C.4. Similar results were obtained with models related to the imidazole parent type (vide infra)

After several infructuous efforts it was found that the modified parent anthranilbenzylamide (10) can be cleanly cleaved with methanesulfonic acid in 85% yields to the parent anthranilamide (2) which then becomes available to start another cycle.

The general applicability of this type of template synthesis has been demonstrated in many ways. Thus, the reaction of 3-acetonyl 4-quinazolone (7) with benzylamine and p-TsOH, under conditions described above, gave the derived product 1-benzyl 5-methyl imidazole (9), mp 99°C in 55% yields (overall yield from anthranilamide 23.6%) and the modified parent (10) (45%).

9: mp : 99°C

nmr : $\delta(CDCl_3)$, 60 MHz . 2.1 (s, 3H, $-C\underline{H}_3$), 5.05 (s, 2H, $-C\underline{H}_2Ph$), 6.85-8.2 (m, 7H, aromatic)

m/z : 172 (M^+).

The selective formation of specifically 5-substituted N-protected imidazoles by the template strategy provides the best route to such compounds. In spite of the continuing interest in imidazoles[7], the procedures for the synthesis of such N-protected 5-substituted imidazoles are scarce and pathways cumbersome. This aspect is best exemplified by the procedure that is currently recommended for the preparation of 1-benzyl 5-methyl imidazole (9) *via* the lengthy sequence: D-fructose ⟶ 4(5)-hydroxymethyl imidazole → 1-benzyl 4-hydroxymethyl imidazole + 1-benzyl 5-hydroxymethyl imidazole, chromatographic separation of the desired 5-isomer, halogenation with $SOCl_2$ and reduction ($Pd/C/H_2$) (overall yield of 9 from fructose < 2%). The 9 thus obtained was identical in all respects to that prepared *via* the cyclic template operation.

The general utility of the template strategy for the preparation of 1-protected 5-substituted imidazoles as well as for a variety of 1-substituted imidazoles has been further established.

The reaction of 6 with octadecylamine in refluxing xylene, promoted by p-TsOH, gave the daughter product, 1-octadecyl 5-phenyl imidazole (11, 32%) with simultaneous formation of the anthraniloctadecyl amide (13, 35%) (CHART I.C.4). In an analogous manner, compound 7 when

processed through the cycle gave 1-octadecyl 5-methyl imidazole (12, 18%) and 31% of 13. The novel lipids 11 and 12 are of interest since they carry the biologically important imidazole unit. Micellar systems involving either 11 or 12 are therefore expected to show novel catalytic profile in imidazole mediated reactions.

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11. Low melting solid

nmr : $\delta(CDCl_3)$, 60 MHz : 0.6-1.75 (m + s, 35H, $-CH_2-(CH_2)_{16}-CH_3$), 3.95 (t, 2H, $-CH_2-(CH_2)_{16}-CH_3$), 6 95-7.85 (m + s, 7H, aromatic)

m/z 396 (M^+)

12. Low melting solid

nmr : $\delta(CDCl_3)$, 60 MHz : 0.65-1.8 5 (m, 35H, $-CH_2-(CH_2)_{16}-CH_3$), 2.27 (s, 3H, $-CH_3$), 3.80 (t, 2H, $-CH_2-(CH_2)_{16}-CH_3$), 7.35 (s, 1H, aromatic)

m/z : 334 (M^+)

13 mp : 86-87°C

ir : ν_{max}(KBr) cm^{-1}, 3500, 3400 (NH_2), 3330 (-NH), 1640 (-CO), 1590, 1550 (C=C, C=N).

nmr : $\delta(CDCl_3)$, 60 MHz, 0.63-1.73 (m + s, 35H,

$-CH_2$ $(C\underline{H}_2)_{16}-C\underline{H}_3$), 3.33 (m, 2H, $-C\underline{H}_2-(CH_2)_{16}$ $-CH_3$), 5.2 (s, 2H, $N\underline{H}_2$), 6.05 (br, 1H, $-CON\underline{H}$), 6.43-7.43 (m, 4H, aromatic).

Further, compound 6 when reacted with cyclohexyl amine and p-TsOH in the usual manner gave the expected derived product 1-cyclohexyl 5-phenyl imidazole (14) in 70% yields and a 50% yield of the modified parent anthranilcyclohexyl amide (15).

14: bp : 180°/0.1 torr

nmr : δ($CDCl_3$), 60 MHz, 1-2.35 (m,10H, $-C_6\underline{H}_{11}$), 3.85 (br, 1H, $-C_6\underline{H}_{11}$), 7.35 (br, s, 7H, aromatic)

m/z : 226 (M^+)

15: mp : 154°C

ir : ν_{max}(KBr) cm^{-1}: 3470, 3360 (NH_2), 3290 (-NH), 1620 (amidecarbonyl)

nmr : δ($CDCl_3$), 60 MHz, 0.6-2.3 (m,10H,$-C_6\underline{H}_{11}$), 3.85 (br, 1H, $C_6\underline{H}_{11}$), 5.5 (br, 2H, $-N\underline{H}_2$), 5.9 (br, 1H, $-CON\underline{H}$), 6.4-7.3 (m, 4H, aromatic).

The reactions thus far described using anthranilamide as the template is presented in CHART I,C.4.,

Numerous experiments were carried out to extrapolate the sequence of events represented in CHART I.C.4, to extend the template synthesis to further substituted imidazoles and other heterocyclic systems. The results thus far are not encouraging, excepting, perhaps, for the possibility of effecting functionalised 1,2,4-triazoles (vide infra). These endeavours are briefly summarized below.

The 2-methyl analogs of 7 and 6, namely, 2-methyl 3-acetonyl 4-quinazolone (37) and 2-methyl 3-phenacyl 4-quinazolone (38) were prepared by alkylation of 2-methyl 4-quinazolone (36) [please see Part II of the thesis][8]. The reaction of either 37 or 38 with benzylamine and p-TsOH, under conditions that led to efficient formation of derived products in the case of the 2-unsubstituted analogs, resulted largely in the recovery of starting materials. This finding, in conjunction with similar studies with the model system 3-methyl 4-quinazolone (35) (vide supra) would mean that the required Schiff base/enamine formation does not occur easily in compounds 37 and 38.

In an endeavour to generate 5-phenyl oxazole as the derived product, compound 6 was refluxed in xylene in the presence of hexamethyl disilazane (HMDS) and p-TsOH; no

reaction was observed. Similar unreactivity was found when 3-benzamido 4-quinazolone[9] was reacted with HMDS/p-TsOH.

It was envisaged that the thio carbonyl analogs of 6 and 7 would show proclivity for addition to the 4-quinazolone 1,2-bond, that would result in the formation of derived thiazoles. However, attempted C=O → C=S change with P_2S_5 in dry benzene with compound 7 gave complex mixtures. An effort was made to improve the prospects by the use of p-anisyl thionophosphine sulphide[10] as the reagent for the generation of the thio carbonyl unit. In this event also, with the phenacyl compound 6, the reaction resulted in mixtures.

In principle, 4-quinazolones, substituted with an amidine unit at the 3-position should be capable of undergoing reactions analogous to that described in CHART I.C.4 leading to 1,2,4-triazoles as derived products. This unit was sought from 3-benzamido 4-quinazolone[9], 2-methyl 3-benzamido 4-quinazolone (56) and 2-phenyl 3-benzamido 4-quinazolone (61) *via* transformation of the ligand amide unit to an imino chloride with $POCl_3$ followed by displacement with benzyl amine. This series of reactions gave complicated mixtures in all the three cases studied.

Encouraging results have been obtained from studies of the reaction of 3-amino 4-quinazolone[11] with dicyclohexyl

carbodiimide. In this case the expected adduct could be obtained, although its isolation in a pure state posed problems. This adduct, on thermolysis, gave the expected derived product, namely, 3-cyclohexylamino 4-cyclohexyl 1,2,4-triazole, whose structure was confirmed by mass spectral data. However, the nmr of the compound indicated the presence of aromatic impurities. The high reactivity of the triazole, coupled with the possible generation of other reactive compounds during thermolysis, could account for the observed complexity. Nevertheless, it appears reasonable to conclude that 4-quinazolones having an amidine grouping attached to the 3-position could lead to derived 1,2,4-triazoles.

The cyclic operations with anthranilamide (CHART I.C.4) illustrate that aspect of the ATP-imidazole cycle which involves the directed synthesis of an imidazole using a soluble template. Another facet of the Natural cycle which is aesthetically more pleasing is the generation of a daughter imidazole from a parent imidazole template. This has been accomplished starting from 1-benzyl 5-amino-imidazole-4-carboxamide (1) (CHART I.C.5).

1-Benzyl 5-amino imidazole 4-carboxamide (1) was transformed to 9-benzyl hypoxanthine (3) in 67% yields, by a modified procedure, by treatment with $HCONH_2$ at 195°C.

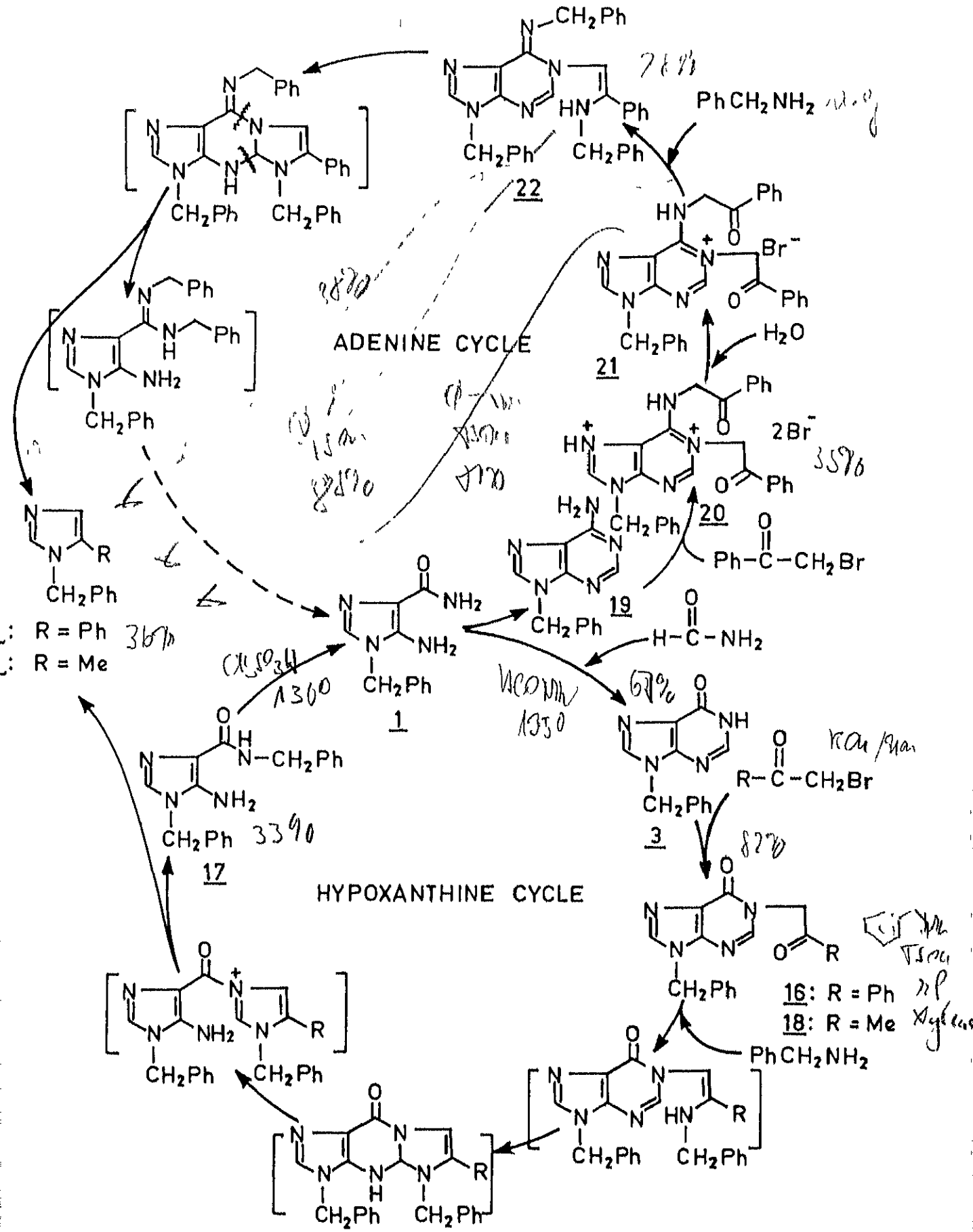
3.	mp :	291°C
	ir	ν_{max} (KBr) cm^{-1}, 1700 (amide carbonyl), 1590, 1550, 1520 (C=C, C=N)

Compound 3 was converted to its conjugate base by treatment with 1.5 equivalents of KOH in EtOH and then reacted with 2 equivalents of phenacyl bromide to give 1-phenacyl 9-benzyl hypoxanthine (16) in 82% yields. The structural assignment for 16 is supported by spectral and analytical data.

16:	mp :	201°C
	ir :	ν_{max} (KBr) cm^{-1}; 1700 (-CO), 1610, 1590 (C=C, C=N)
	nmr :	$\delta(CDCl_3)$, 60 MHz: 5.3 (s, 2H, $-C\underline{H}_2COPh$) 5.5 (s, 2H, $-C\underline{H}_2Ph$), 7.2-8.2 (m, 12H, aromatic)
	m/z :	344 (M^+), 239 (M^+ - PhCO).

Compound 16 proceeded through the cycle (CHART I.C.5), on reaction with 4 equivalents of benzylamine and 3 equivalents

CHART I.C.5


ADENINE CYCLE
HYPOXANTHINE CYCLE
22
21
20
19
1
3
17
16: R = Ph
18: R = Me
PhCH2NH2
H2O
2Br⁻
Br⁻
CH2Ph
NH2
NH
HN
O
N
R = Ph
R = Me

of p-TsOH in refluxing xylene for 12 hours to yield 36% of the daughter product 1-benzyl 5-phenyl imidazole (8) and 33% of the modified parent 5-amino 1,N-dibenzyl imidazole 4-carboxamide (17). The derived product 8 from this cycle was identical to that obtained earlier (vide supra).

17: mp : 159-160°C

ir : ν_{max}(KBr) cm^{-1}; 3400, 3300 (NH_2, NH), 1630 (amide carbonyl)

nmr : $\delta(CDCl_3)$, 60 MHz· 4.45 (d, 2H, $-CONHC\underline{H}_2Ph$, + D_2O, s), 4.7 (br, 2H, $-N\underline{H}_2$, exch.D_2O), 4.8 (s, 2H, $-C\underline{H}_2Ph$), 6.8-7.7 (m, 12H, $-N\underline{H}$ and aromatic)

m/z · 306 (M^+).

The sequence of events leading to daughter products from the imidazole template 1 (CHART I.C.5) is analogous to that presented in CHART I.C.4 for the anthranilamide mediated template reaction. Additional support for the sequence of events in such operations have been obtained by studies on model systems. Specifically the notion that events leading to the derived products from appropriate alkylated carbonyl precursors are initiated by formation of Schiff bases/enamines

via reaction with appropriate amines is re-inforced by the recovery of 1,9-dibenzyl hypoxanthine (*42*)[12] on treatment with benzylamine and p-TsOH under conditions of template synthesis.

The importance of acid catalysis for the sequence of events associated with these cyclic processes has been brought out by the attempted transformation of *16* to derived product and modified parent with benzylamine in the absence of p-TsOH. This reaction gave neither *8* nor *17*.

The modified parent *17* was cleanly transformed to the parent template *1*, which becomes then available to initiate the second cycle, upon treatment with methane sulphonic acid at 130°C for 3 hours.

The potassium salt of 9-benzyl hypoxanthine (*3*) generated with MeOH-KOH on treatment with 2 equivalents of bromoacetone gave in 66% yields 1-acetonyl 9-benzyl hypoxanthine (*18*).

18: mp : 155-158°C

ir : ν_{max}(KBr) cm^{-1}; 1715 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz: 2.25 (s, 3H, $-C\underline{H}_3$), 4.95 (s, 2H, $-C\underline{H}_2-$), 5.3 (s, 2H, $-C\underline{H}_2Ph$), 7.3 (s, 5H, aromatic), 7.95 (s, 1H, imidazolyl proton , 7.95 (s, 1H, pyrimidyl

proton)

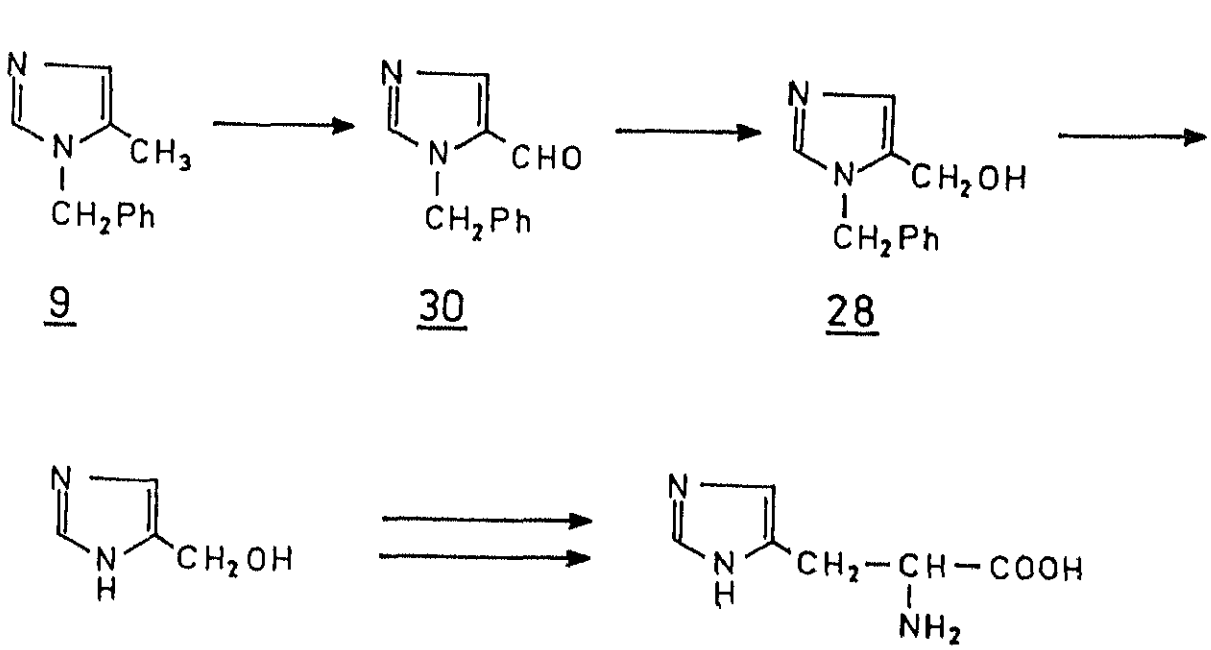
m/z 282 M^+, 239 ($M^+ - COCH_3$).

Compound 18 when admixed with 4 equivalents of benzylamine and 3 equivalents of p-TsOH and refluxed in dry xylene for 12 hours gave 30% of the daughter product 1-benzyl 5-methyl imidazole 9 and 26% of the modified parent 17. Compound 9 obtained in this experiment was identical to an authentic sample.

In the ATP-Imidazole cycle of Nature, the parent 1-phosphoribosyl 5-amino imidazole 4-carboxamide leads to, as the daughter product, 5-imidazole glycerol phosphate, which is then transformed to histidine. In order to provide a fuller perspective of the simulation studies, it was considered desirable to transform 1-benzyl 5-methyl imidazole (9), the daughter product arising from the template 1-benzyl 5-amino imidazole 4-carboxamide 1, also to histidine.

The obvious linkage between the template product 1-benzyl 5-methyl imidazole (9) and histidine (34) would be 5-chloromethyl imidazole (32), since, this compound has been transformed to 34 by several procedures. The task at hand then was to halogenate the 5-methyl substituent of 9. Direct methods at functionalization of this grouping with reagents

such as N-chloro succinimide and Ph-Se-Cl, gave complex mixtures, perhaps on account of the presence of the benzylic grouping. Consequently, 5-hydroxymethyl imidazole (31) was sought as the link, since this compound has been transformed to chloromethyl compound 32 and then to histidine (34). The reaction of compound 9 with 1 equivalent of SeO_2 in glacial AcOH at reflux for 10 hours gave 1-benzyl 5-formyl imidazole [30, 36%] which was then directly reduced, with $NaBH_4$ in MeOH, to 1-benzyl 5-hydroxymethyl imidazole (28, 61%)[16]. The compound thus obtained was identical in all respects to an authentic sample prepared from D-fructose[13]. Compound 28 was debenzylated by hydrogenation over palladised charcoal leading to the formation of 4(5)-hydroxymethyl imidazole (31) in quantitative yields. The picrate of 31 was found to be identical to that of an authentic sample prepared from D-fructose. The 4(5)-hydroxymethyl imidazole (31) thus obtained was transformed to dl-histidine[14,15] by known procedures. The dl-histidine thus obtained was identical in all respects to that of an authentic sample, thereby completing the link between histidine and the derived product 1-benzyl 5-methyl imidazole (9)[17].



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28 : mp : 134°C (lit.[16] mp 134-135°C)

nmr : δ($CDCl_3$), 60 MHz : 4.46 (s, 2H, $-C\underline{H}_2OH$), 4.7 (s, 1H, $-CH_2O\underline{H}$), 5.14 (s, 2H, $-C\underline{H}_2Ph$), 6.61-7.91 (m, 7H, aromatic)

30 : Low melting solid

ir : ν_{max} (neat) cm^{-1}, 1690 (-CO)

nmr : 5.0 (s, 2H, $-C\underline{H}_2Ph$), 6.73-7.83 (m, 8H, aromatic)

31 : Picrate; mp : 202-203°C (lit.[13] mp 203°C)

34 : mp : 268-269°C (lit.[14,15] mp 273°C)

From the above account it could be discerned that facets pertaining to the chemical simulation of ATP-Imidazole cycle (CHART I.C.1) were developed in stages and with increasing relevance to the Natural cycle. An aspect that has hitherto not been examined in the simulation studies is the use of an appropriately protected adenine as a key intermediate. It could be seen from CHART I.C.1 that although hypoxanthine is an integral part of the cycle, it is transformed to adenine prior to alkylation. Template studies with adenine were deferred to a later stage in view of the significantly higher reactivity of this compound compared to hypoxanthine and the need to have information pertaining to the alkylation of adenine, which was obtained from model studies.

The reaction of the sodium salt of adenine with benzylbromide, as reported[18], gave in 27% yields, 9-benzyl adenine (19).

19: mp : 232-233°C

ir : ν_{max} (KBr) cm^{-1}: 3460, 3340 ($-NH_2$)
1660, 1610 (C=C, C=N)

nmr : δ(DMSO-d_6), 100 MHz : 5.4 (s, 2H, $-C\underline{H}_2Ph$),
7.3 (m, 5H, phenyl), 8.0 (s, s, 1H, 1H, 2,8-purine ring).

9-Benzyl adenine (19) on treatment with 1.5 equivalents of phenacyl bromide in dry DMF gave colourless prisms mp 219-223°C, to which, based on spectral and analytical data, the bis salt structure 20 (CHART I.C.5) has been assigned. The yield of 20 was 35% and no other pure products could be obtained from this reaction, which has been carried out several times.

20: mp : 219-223°C

ir : ν_{max} (KBr) cm^{-1}: 3420, 3060, (-NH), 1690 (-CO), 1630, 1600 (C=C, C=N)

The formation of the bis salt (20) is surprising, since, during model studies when 9-benzyl adenine (19) was treated with benzyl bromide under similar conditions only the 1-monoalkylated product was obtained.

The reaction of 20 with hot water for a brief period, conditions under which the model system, 1,9-dibenzyladenine hydrobromide hydrolyses to the neutral 6-imino 1,9-dibenzyl adenine, gave the monohydrobromide 21 (92%). The structural assignment for 21 is fully supported by spectral and analytical data.

21:	mp :	225-228°C
	ir :	ν_{max} (KBr) cm^{-1}; 3460, 3020 (-NH), 1710 (-CO), 1660, 1600 (C=C, C=N)
	^{1}H nmr :	δ(DMSO-d_6), 200 MHz . 5.05 (s, 2H, -C$\underline{H}_2$COPh), 5.7 (s, 2H, -C$\underline{H}_2$Ph), 6.4-7.1 (m, 16H, phenyl), 7.35 (d, J = 8 Hz, 2H, -NHC$\underline{H}_2$COPh), 7.91 (s, 1H, 6-purine proton), 8.75 (s, 1H, 2-purine proton).
	^{13}C nmr .	δ(DMSO-d_6): 190 8 (carbonyl), 145.5, 136.0, 134.7, 134.5, 133.9, 133.8, 131.6, 129 1, 128.9, 128 7, 128.3, 125.6, 114.1, 109 59, 55 7 (-CH_2), 49.1 (-CH_2)

Compound 21 is structurally analogous to the similar alkylated adenine of the Natural ATP-Imidazole cycle (CHART I.C.1). Consequently, it was anticipated that this compound could be processed through the cycle to yield derived products. This expectation was realized. Thus, compound 21 when held at reflux for 4 hours with 4 equivalents of benzylamine gave, in 38% yields, the daughter product, 1-benzyl 5-phenyl imidazole (8). Of significance was the isolation of another crystalline compound, mp 136-138°C, for which, based on spectral and analytical data, structure 22

has been assigned. The yield of this compound was 28% (CHART I.C.5).

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22 : mp : 136-138°C

ir : ν_{max}(KBr) cm^{-1}, 3240 (NH), 1630 (C=N)

nmr $\delta(CDCl_3)$, 60 MHz, 3.7 (m, 2H, NH-C<u>H</u>$_2$-Ph, D_2O, q) 4.22 (s, 2H, =N-C<u>H</u>$_2$-Ph), 4.75 (s, 1H, -C<u>H</u>-C(NH-)-Ph), 4.85 (s, 1H, C<u>H</u>$_2$Ph), 5.2 (m, 1H, N<u>H</u> exch. with D_2O), 7.2-8.0 (m, 23H, aromatic).

m/z : 522 (M^+).

The isolation and characterization of compound 22 is noteworthy, in the sense that similar structures have been envisaged as crucial intermediates, towards formation of derived products with parent template, anthranilamide (2) (CHART I.C.4) as well as 1-benzyl 5-amino imidazole 4-carboxamide (1) (CHART I.C.5). Support for this conjecture was obtained by treatment of compound 22 with 4 equivalents of benzyl amine and 1 equivalent of p-TsOH in refluxing xylene for 12 hours. Most gratifyingly, this experiment gave in excellent (88%) yields, the expected daughter product 1-benzyl 5-phenyl imidazole (8)[19]. The formation of compound

22 and the derived product 8 on treatment of 21 with benzylamine coupled with the clean transformation of 22 → 8 described above, strongly support the intermediacy of a parent-daughter tricyclic system that is believed to undergo rupture to the modified parent and the derived product (CHART I.C.4 and CHART I.C.5). Further, these observations bring out the importance of p-TsOH in the efficient transformation of such intermediates to derived products. This notion derives support from the finding that the monosalt 21 when refluxed in dry xylene with 4 equivalents of benzylamine and 2 equivalents of p-TsOH for 12 hours, gave a 71% yield of the derived product 8, none of the intermediate 22 could be detected (tlc)[20].

The transformation of 21 to derived products can be expected to be general; this has been demonstrated by reaction of 21 with 6 equivalents of cyclohexylamine and 2 equivalents of p-TsOH in refluxing xylene for 18 hours leading to the isolation of the derived 1-cyclohexyl 5-phenyl imidazole (14) in 49% yields.

An integrated picture of the present endeavours relating to the generation of daughter imidazole from the parent imidazole 1 involving alkylation on hypoxanthine as well as adenine are presented in CHART I.C.5. A striking feature of this Chart is the fact that the template operation leading to same daughter product are effective even though the

pathways traversed are structurally quite divergent

The basic requirements pertaining to the chemical simulation of template operations were determined as a result of studies on 4-quinazolones (CHART I.C.4). Indeed, they appear to be superior and more efficient in the generation of derived products compared to the hypoxanthine systems. In sharp contrast, however, although, as described above, derived products could be obtained from 9-benzyl adenine (19) the related model, namely, 4-amino quinazolone (23) failed.

Interestingly, whilst the primary products for parent templates described thus far, namely, 4-quinazolone (4), 9-benzyl hypoxanthine (3) and 9-benzyl adenine (19) are available by simple procedures, the preparation of 4-amino quinazoline (23) has to be effected in an indirect manner, via the sequence 4-quinazolone → 4-chloro quinazoline → 4-phenoxy quinazoline → 4-amino quinazoline (23) with an overall yield of 43%.

The reaction of 4-amino quinazoline (23) with 1.5 equivalents of phenacyl bromide in dry DMF gave colourless crystals, mp 283-288°C to which, based on spectral and analytical data, structure 24 has been assigned. The yield of 24 was 68%. Thus, this reaction gave the 3N-alkylated product without the complexities that was observed earlier in the case of 9-benzyl adenine (vide supra). The alkylation

pattern in the 23 → 24 change is analogous to that of 9-benzyl adenine (19) with benzyl bromide (vide supra)

24: mp : 283-288°C

ir : ν_{max} (KBr) cm^{-1}, 3360, 3260, 3060, (amide NH), 1695 (-CO), 1675, (amide carbonyl)

nmr : δ (DMSO-d_6): 5.5 (s, 2H, -CH_2COPh), 6.7-7.3 (m, 8H, (aromatic), 7.68 (d, J = 8 Hz, 1H), 8.0 (s, 1H, 2-quinazolyl proton).

Compound 24, being structurally similar to 21 that smoothly gave derived products, could be anticipated to proceed through the cycle on treatment with amines leading to derived products. In the event, the reaction of 24 with benzylamine and p-TsOH resulted in a complex mixture, which did not contain (tlc) the expected daughter product, 1-benzyl 5-phenyl imidazole (8).

It was envisaged that compound 24 on treatment with hot water, would give rise to the neutral 4-imino 3-phenacyl quinazoline, in a manner similar to the 1,9-dibenzyl adenine salt (vide supra). Further, this imino compound can be transformed to derived products by pathways similar to that of the Natural cycle (CHART I.C.1) or via those with either anthranilamide (CHART I.C.4) or 1-benzyl 5-amino imidazole

4-carboxamide (1) (CHART I.C.5) as parent templates.

However, the reaction of 24 with hot water under conditions of the 20 → 21 change took an unexpected and hitherto unencountered course leading to, in 77% yields, the isomeric salt 25, mp 306-311°C whose structure is fully supported by spectral and analytical data. The 24 → 25 change can be readily understood on the basis of the sequence, addition of water at the 2-position, rupture of the 2,3 bond and recyclization (Dimroth rearrangement[21]) (CHART I.C.6).

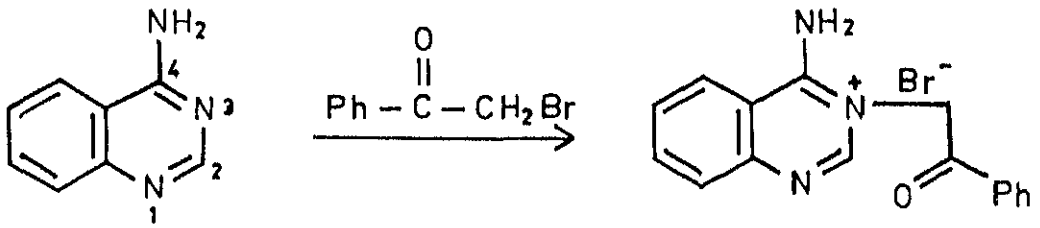
25: mp : 306-311°C

ir : ν_{max}(KBr) cm^{-1}: 3260, 3060 (amide NH), 1690 (-CO), 1675, 1585 (C=C, C=N)

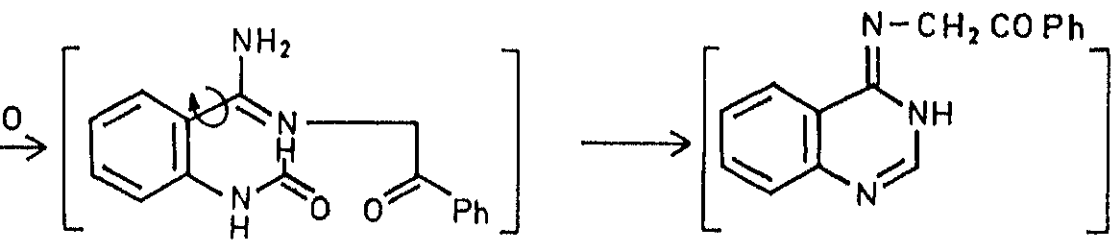
m/z : 263 (M^+ - HBr)

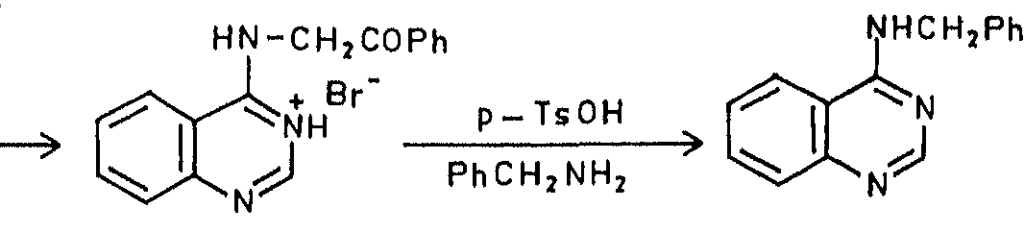
The widely divergent behaviour shown by 20 and 24 towards water is noteworthy. The instability of structure 24 under these conditions must be attributed to the diminished possibilities for dissipation of the positive charge on the nitrogen. It is possible that the absence of formation of derived products on treatment of 24 with benzylamine and p-TsOH is also as a result of addition of the amine to the 1,2 double bond rather than to the carbonyl function. Model

CHART I.C.6



23 24





25 26

studies outlined earlier have demonstrated that 3-substituted 4-quinazolone systems do not add benzyl amine to the 1,2-bond. The rationalization of the success of the 4-quinazolone system, in contrast to the 3N-alkylated 4-amino quinazolines in template synthesis, is based on the divergent behaviour towards amines[22].

The structural assignment for 25 is fully supported by the finding that upon treatment with 5.2 equivalents of benzylamine and 5 equivalents of p-TsOH in refluxing xylene, it gave, a 56% yield of 4-benzylamino quinazoline (26), identical to an authentic sample prepared from 4-chloro quinazoline and benzylamine.

26: mp : 172-173°C

ir : ν_{max}(KBr) cm^{-1}, 3240 (-NH), 1615 (C=N)

nmr : $\delta(CDCl_3)$:, 60 MHz; 4.87 (d, -NH-C$\underline{H}_2$Ph, 2H), 6.47 (br, 1H, -N$\underline{H}$-), 7.12-7.97 (m, 9H, aromatic), 8.46 (s, 1H, quinazolyl proton).

The successful demonstration using appropriate molecular moulds for the production of daughter molecules represents a new strategy in organic synthesis, but not one that is alien to Nature. Such template syntheses allow

wide variations in terms of the parent template, the steps involved in the cyclic operation and the nature of the derived molecules. It was therefore considered appropriate to illustrate such possibilities with handful examples of compounds involving the 1,2 ene-amino acid system or its equivalents as the parent template. This extended analysis is presented below under the heading of "Synthesis on templates: In Prospect".

SYNTHESIS ON TEMPLATES : IN PROSPECT

An interesting reaction of the 1,2-ene- amino ester system, methylanthranilate (70)[23], is the formation of 4-quinazolone 2-thiol in one step with KNCS. Further, it has been shown[24] that alkylation of this compound takes place on the sulphur.

The template synthesis outlined in CHART I.C.7 with the parent template 70 envisages the one step preparation of the S-alkylated product 71 by reaction with KNCS and $PhCOCH_2Br$. Intramolecular cyclization of 71 could be carried out without difficulty, taking advantage of the acidic 3-nitrogen of the 4-quinazolone, leading to the tricyclic system 72 (CHART I.C.7). The transformation of 72 to the template product, 4-phenyl triazole (73) and the parent 70 depends upon the specific reduction of the thio imine unit present. Generally,

electrophilic reducing agents such as diborane are effective in bringing about such a change. Thus, CHART I.C.7 illustrates a feasible strategy for template synthesis of thiazoles.

Parallel to the primary reaction described above, is the effective transformation of anthranilic acid (45) to 3N-liganded 4-quinazolone 2-thiols with alkyl isothiocyanates. For example, the reaction of anthranilic acid and allyl isothiocyanate leads to 3-allyl 4-quinazolone 2-thiol[25]. This compound exhibits a pronounced tendency for sulphur-π participation. Thus, the bromonium or the protonium intermediates generated by acceptance of electrophiles Br^+ or H^+ by the π system are readily neutralized by sulphur participation leading to tricyclic compounds[25]. The template synthesis shown in CHART I.C.8 takes advantage of this property.

The reaction of anthranilic acid 45 with propargyl isothiocyanate can be expected to lead to the quinazolone 74. This compound, in principle, could be transformed to the tricyclic system 75, either involving electrophilic or radical intermediates. As in the earlier illustration, further changes of this compound to the derived product, namely, 5-methyl thiazole (76) and the parent 45 should involve the reduction of the thio imine function present. An attractive feature of this proposal is that the overall function of the template is to fold the molecule that is appropriate to generate the

CHART I.C.7

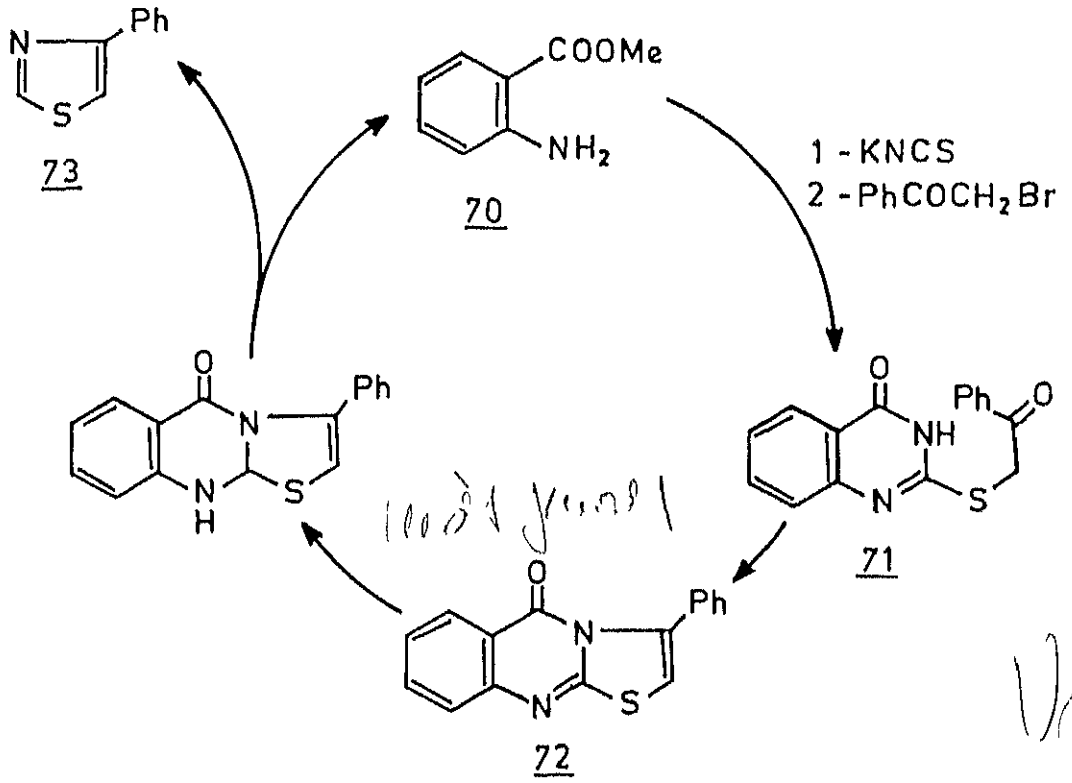
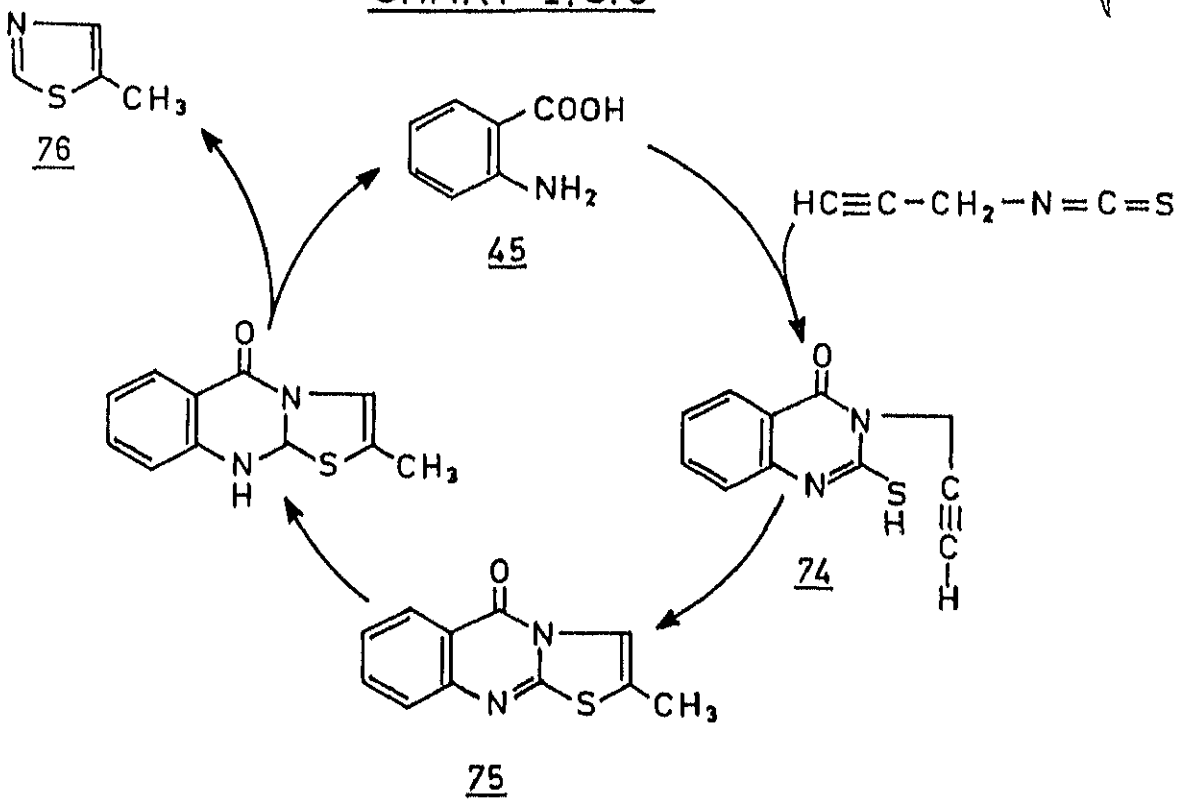


CHART I.C.8

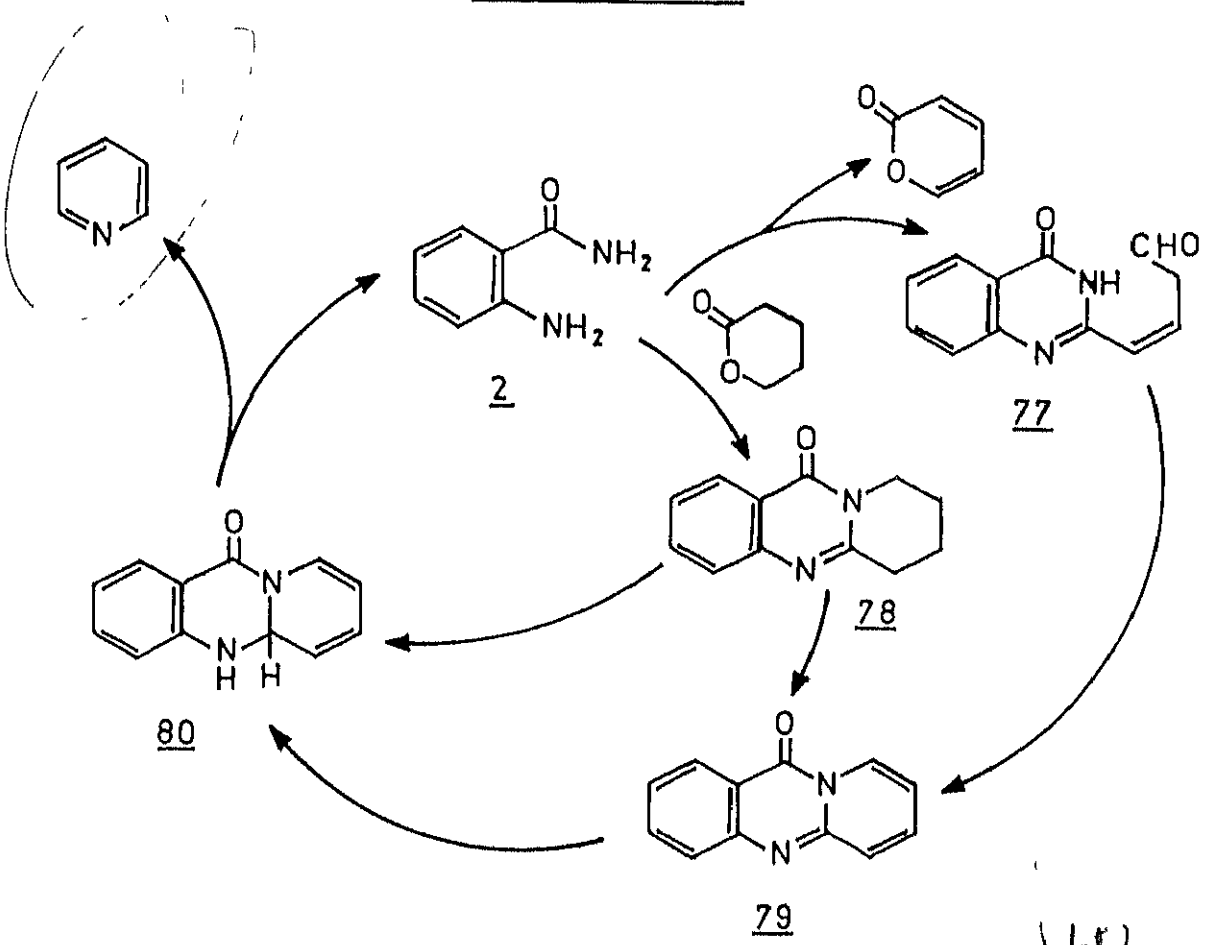


derived products (CHART I.C.8).

The successful template strategies described in the present work and the two envisaged above, all relate to 5-membered heterocyclic systems as derived products. It would be of interest therefore to extend the template strategy for the synthesis of higher membered rings. An obvious route to 6-membered rings as derived products could be discerned on the basis of the reported thermal transformation of anthranilamide (2) with valerolactone. In this interesting reaction, the initially formed 2-liganded 4-quinazolone either cyclises through bonding to 3-position or to the 1-position giving rise to, respectively, linearly or angularly condensed tricyclic systems[26]. However, in view of the known pattern of alkylation specifically at the 3-position by conjugate bases of 4-quinazolone, it should be possible to direct the second cyclization in a linear manner. The adaptability of this reaction to template synthesis is illustrated in CHART I.C.9 giving rise to pyridine as the derived product.

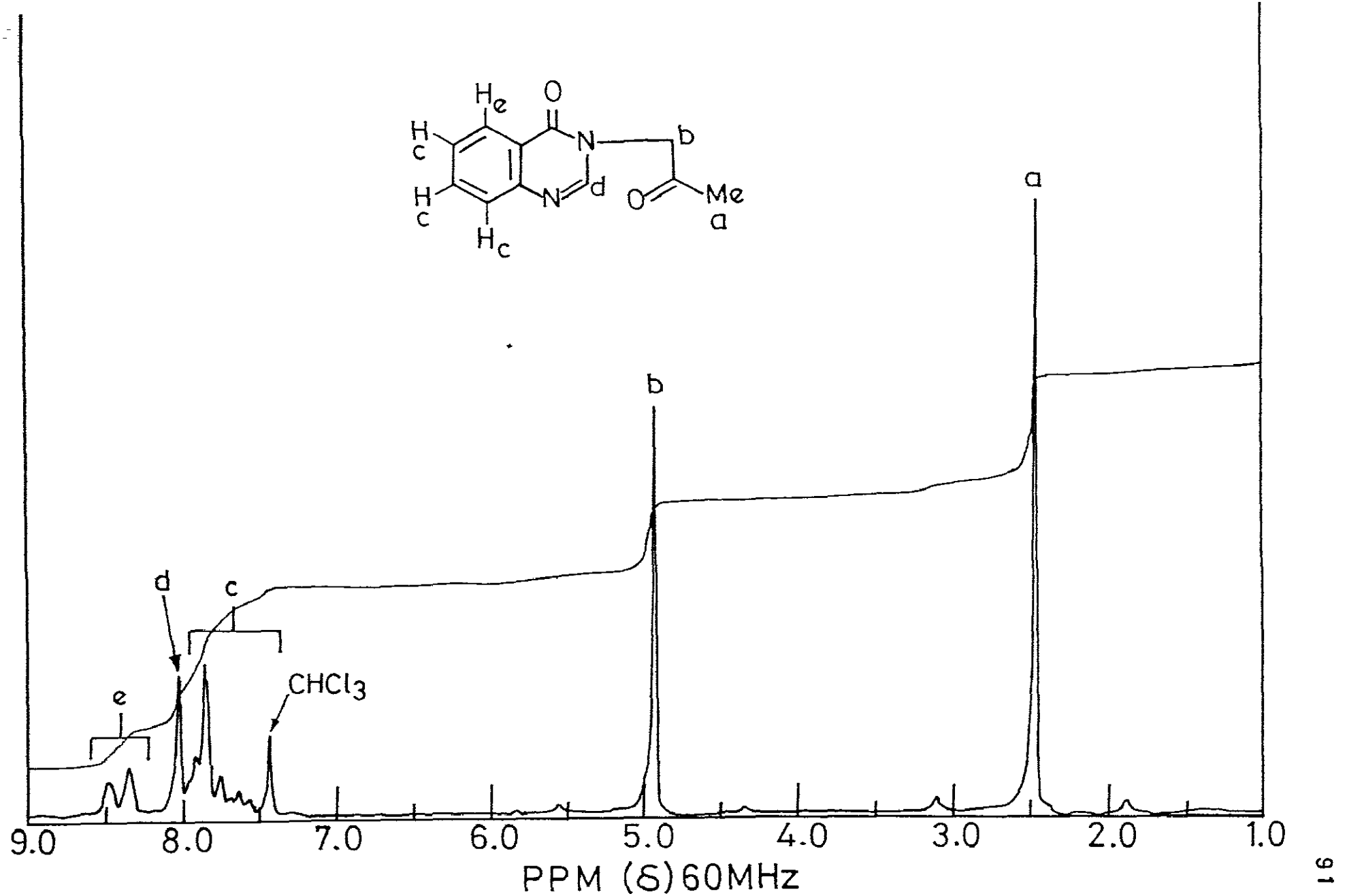
Starting from anthranilamide (2) as template, the strategy outlined in CHART I.C.9 endeavours to realise the formation of derived molecule pyridine by two interconnected pathways. One of these proceeds through the known compound 78, arising from the reaction of 2 with valerolactone. The

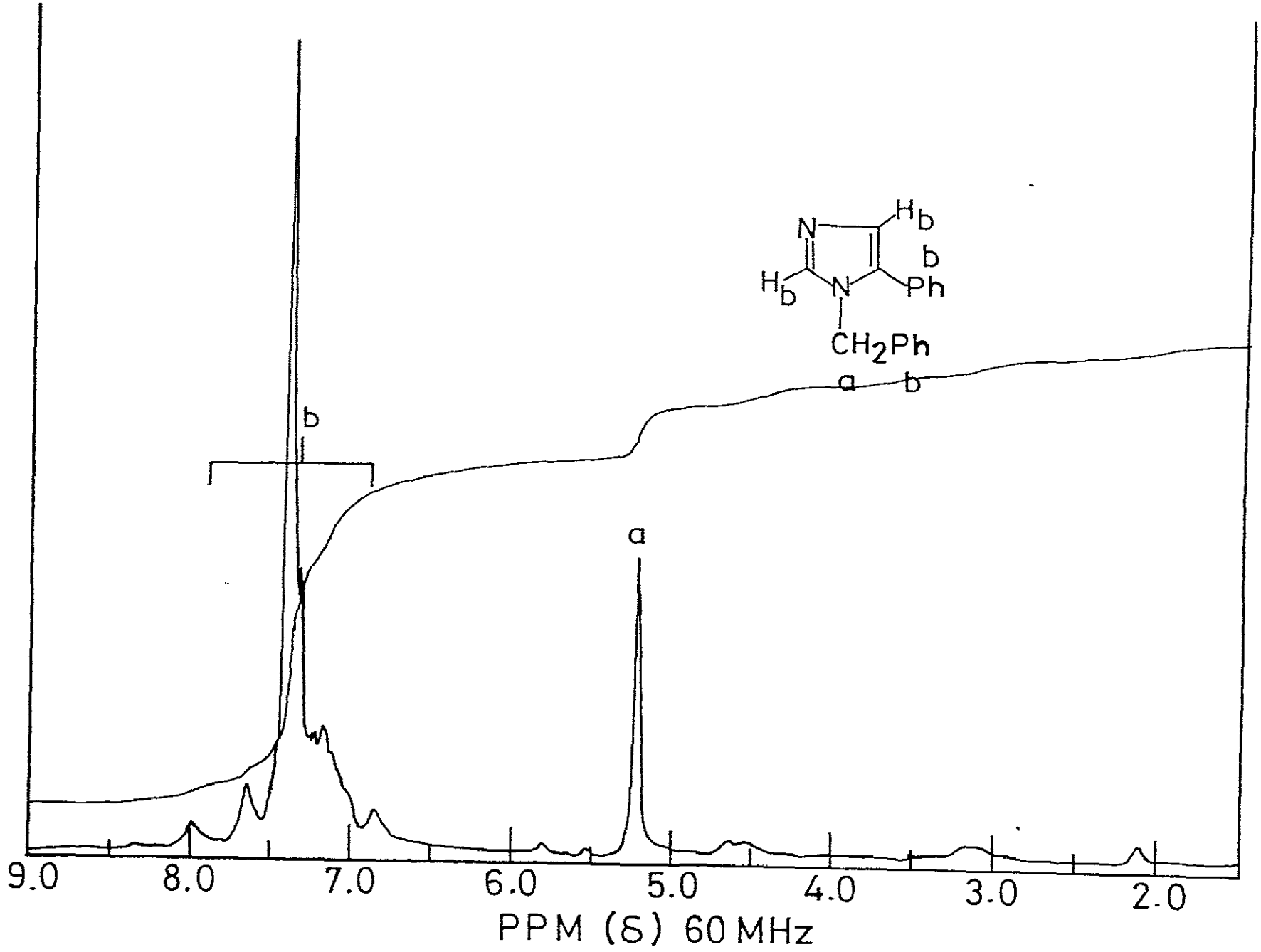
CHART I.C.9

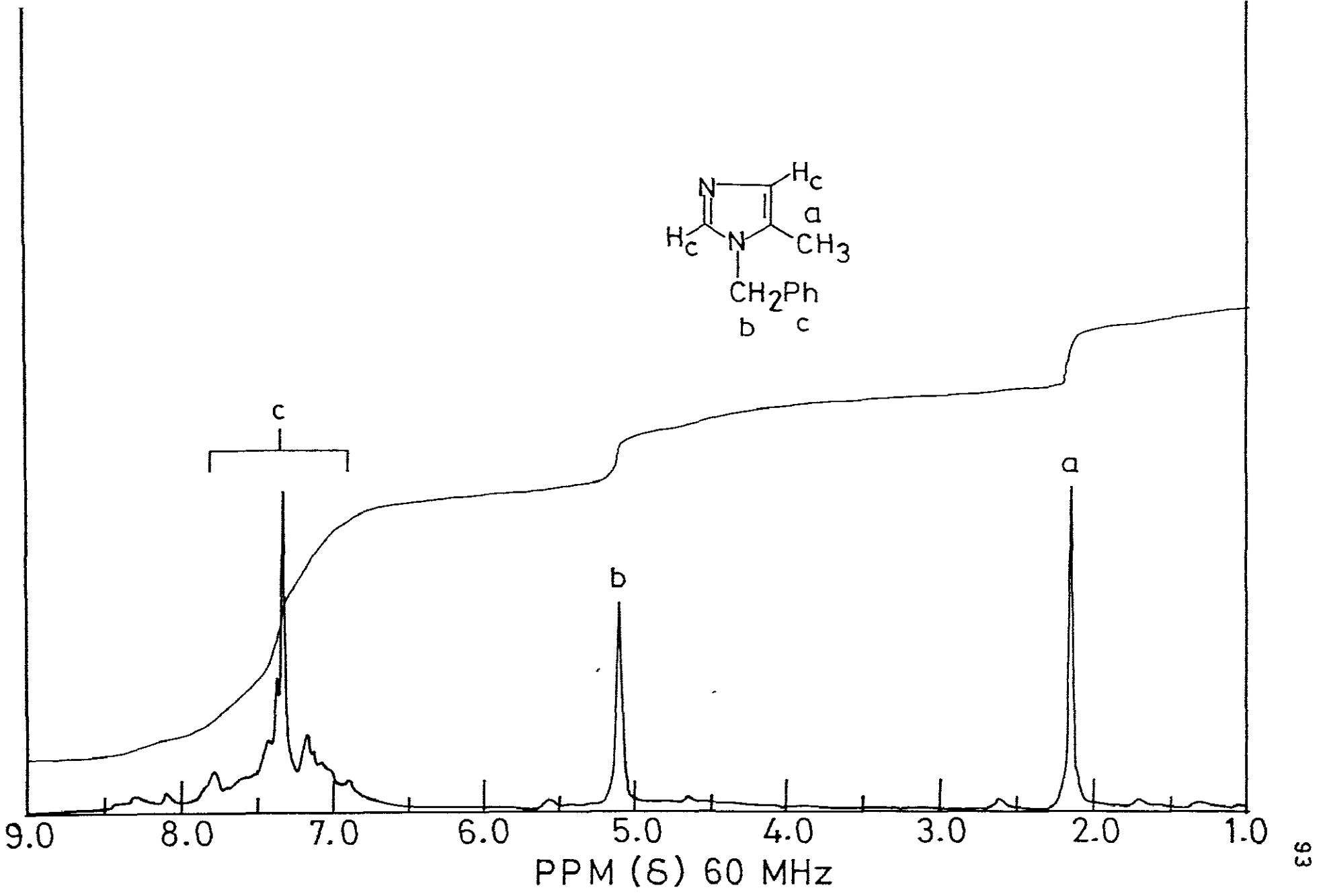


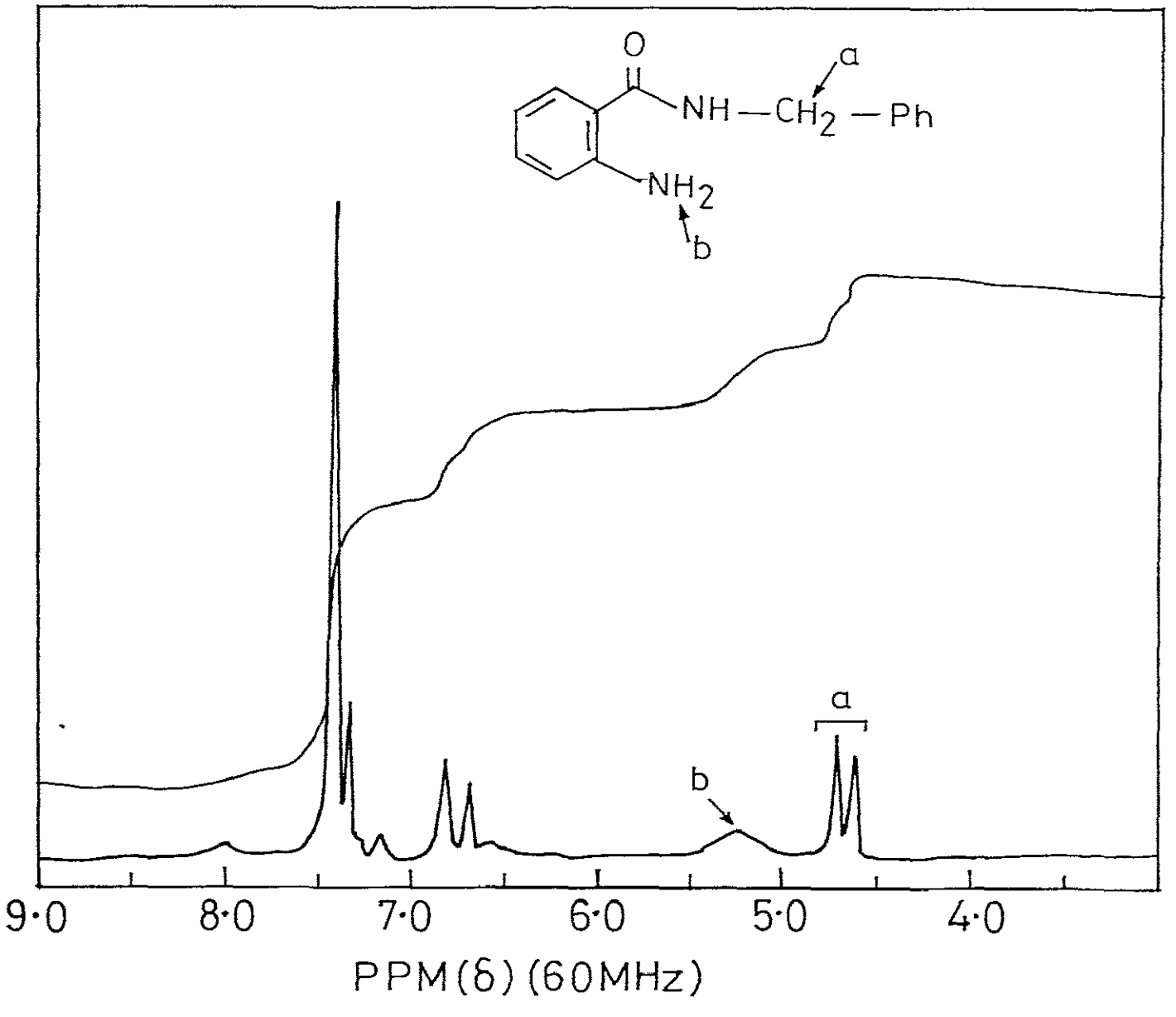
pathways envisaged in the transformation of 78 to the derived product involves either intermediate 79 or 80. The formation of these necessitate dehydrogeneration of 78. A more attractive route is the proposed reaction of 2 with pyran 2-one leading to 77 that would readily cyclize to 79. Selective reduction of the imine group would then lead to the desired tricyclic intermediate 80, which can be expected to fragment readily to pyridine and anthranilamide (2).

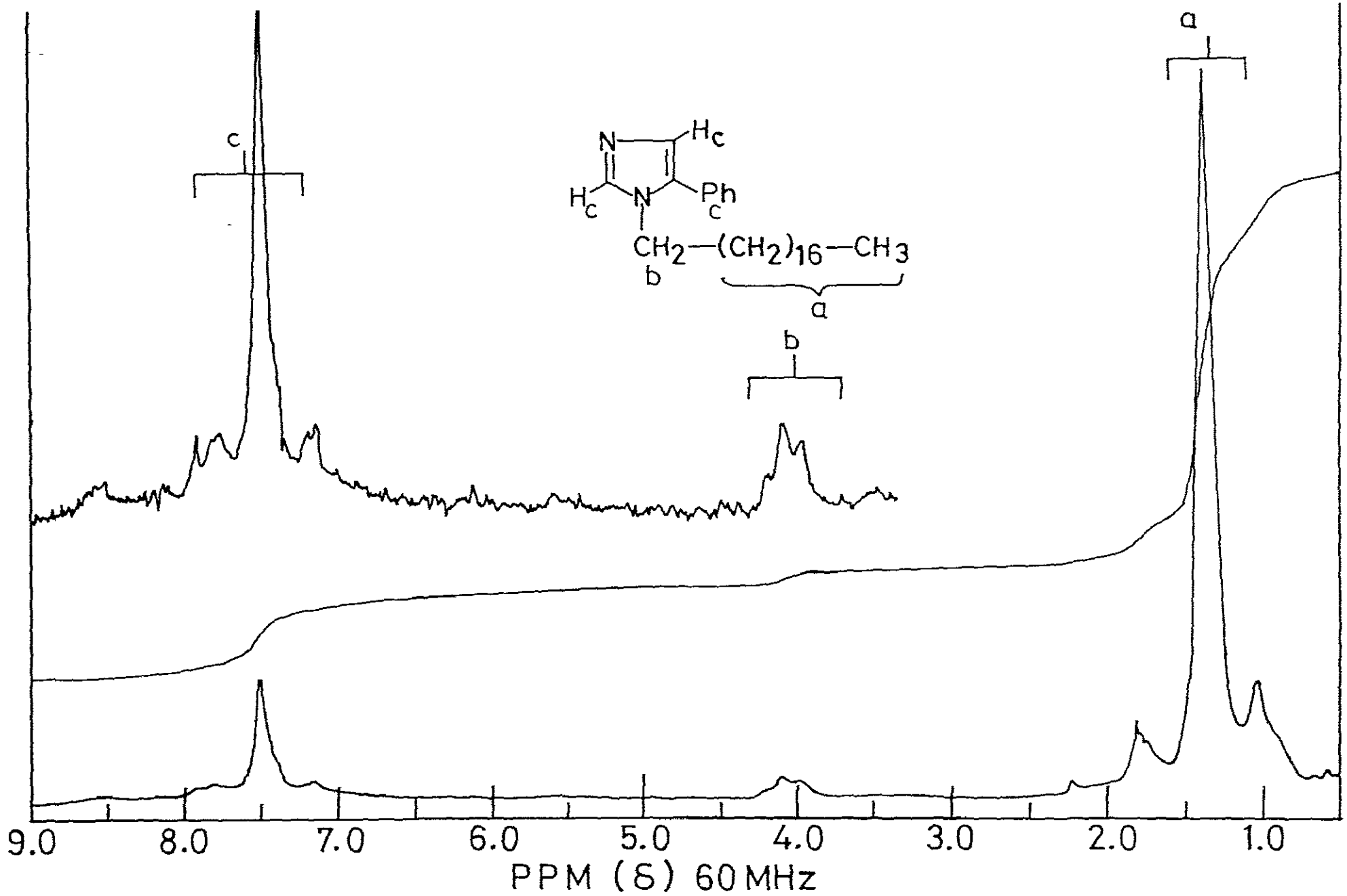
The three schemes proposed in this sub-section hopefully illustrate the wide range of applicability of template mediated synthesis.

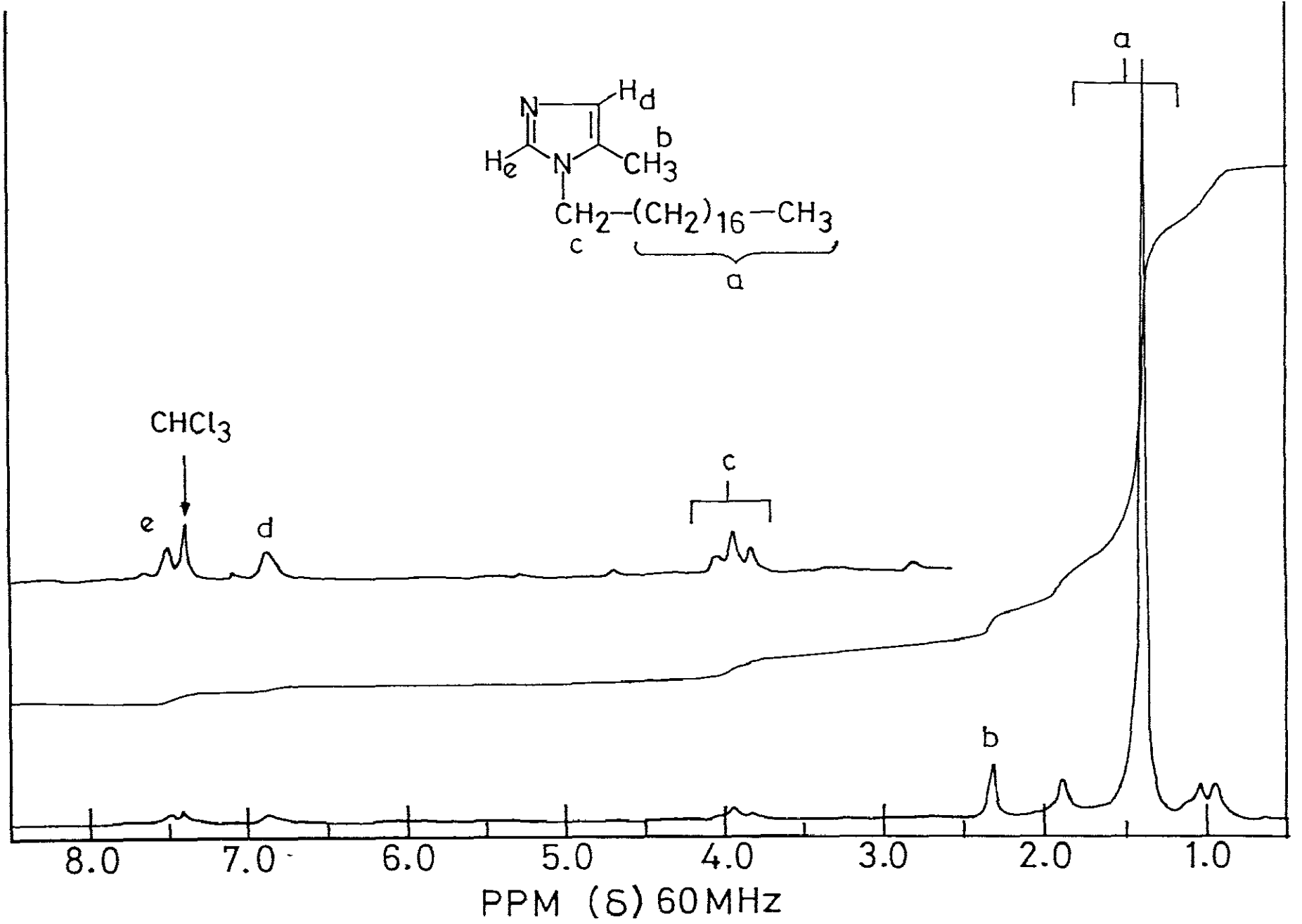

He
O
Hc
N
b
Hc
N
d
O
Me
a
Hc
a
b
d
c
e
CHCl3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60MHz

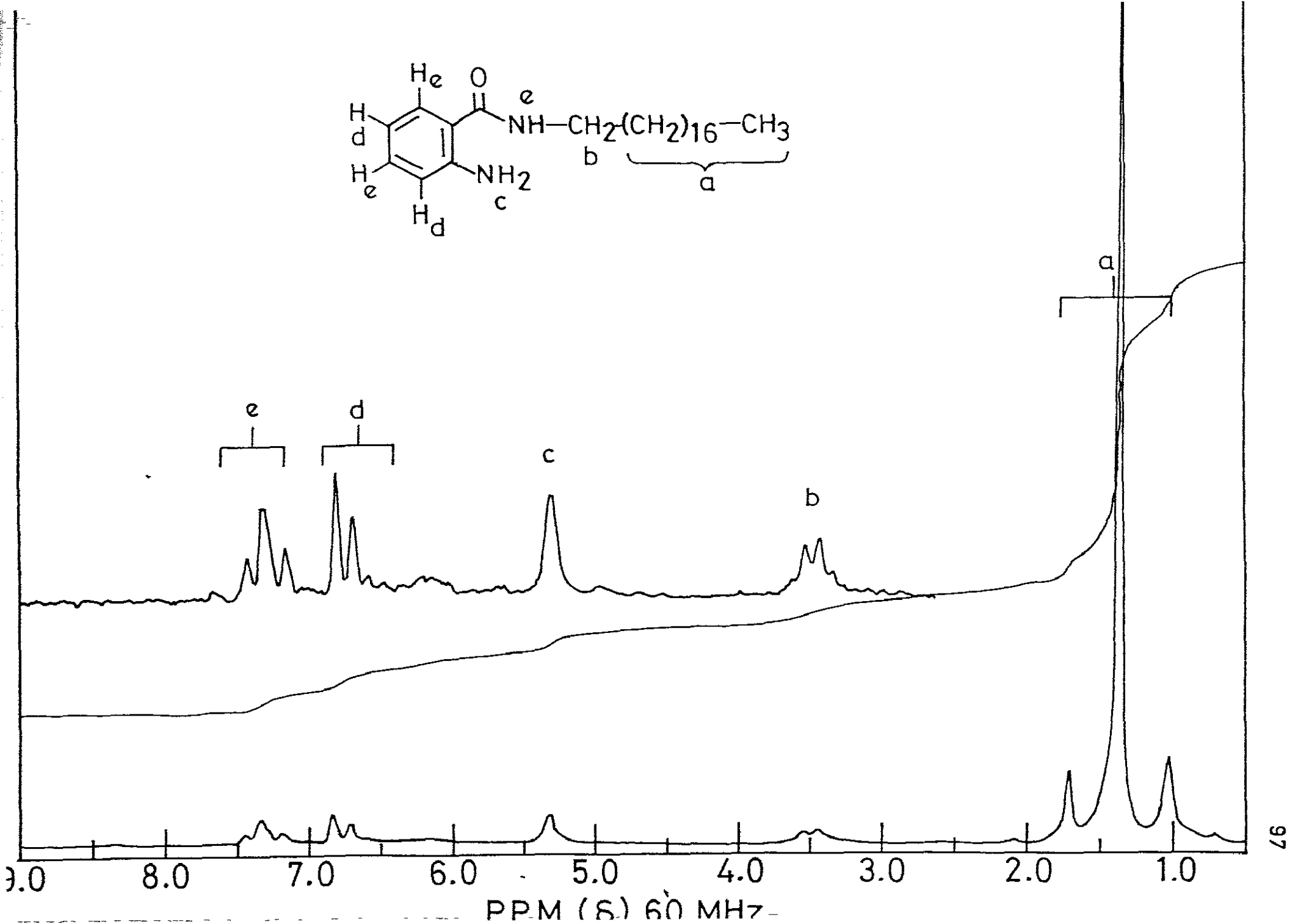

N
Hb
b
Hb
N
Ph
CH2Ph
a
b
b
a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz

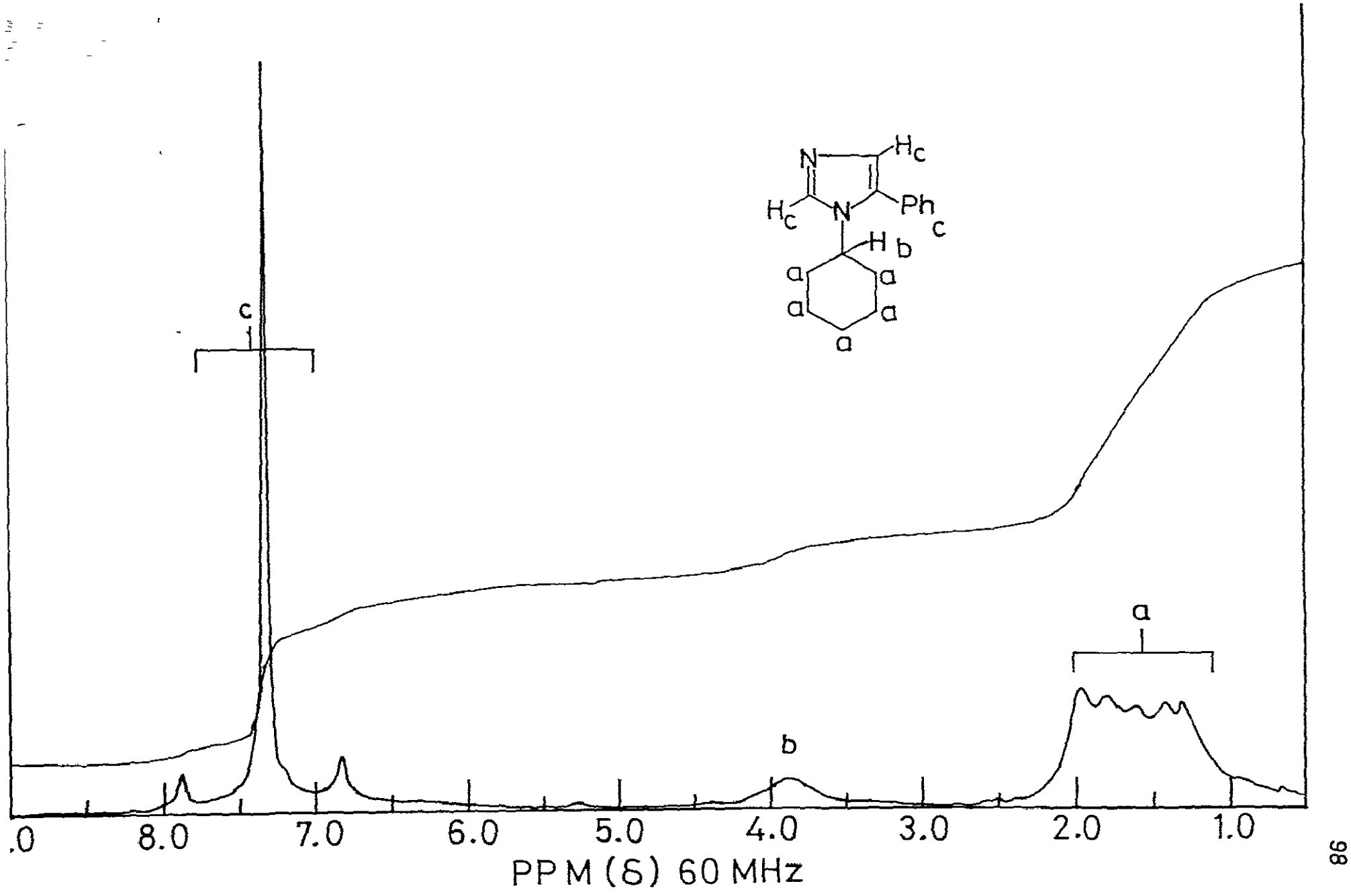

Hc
a
N
Hc
N
CH3
CH2Ph
b c
c
a
b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

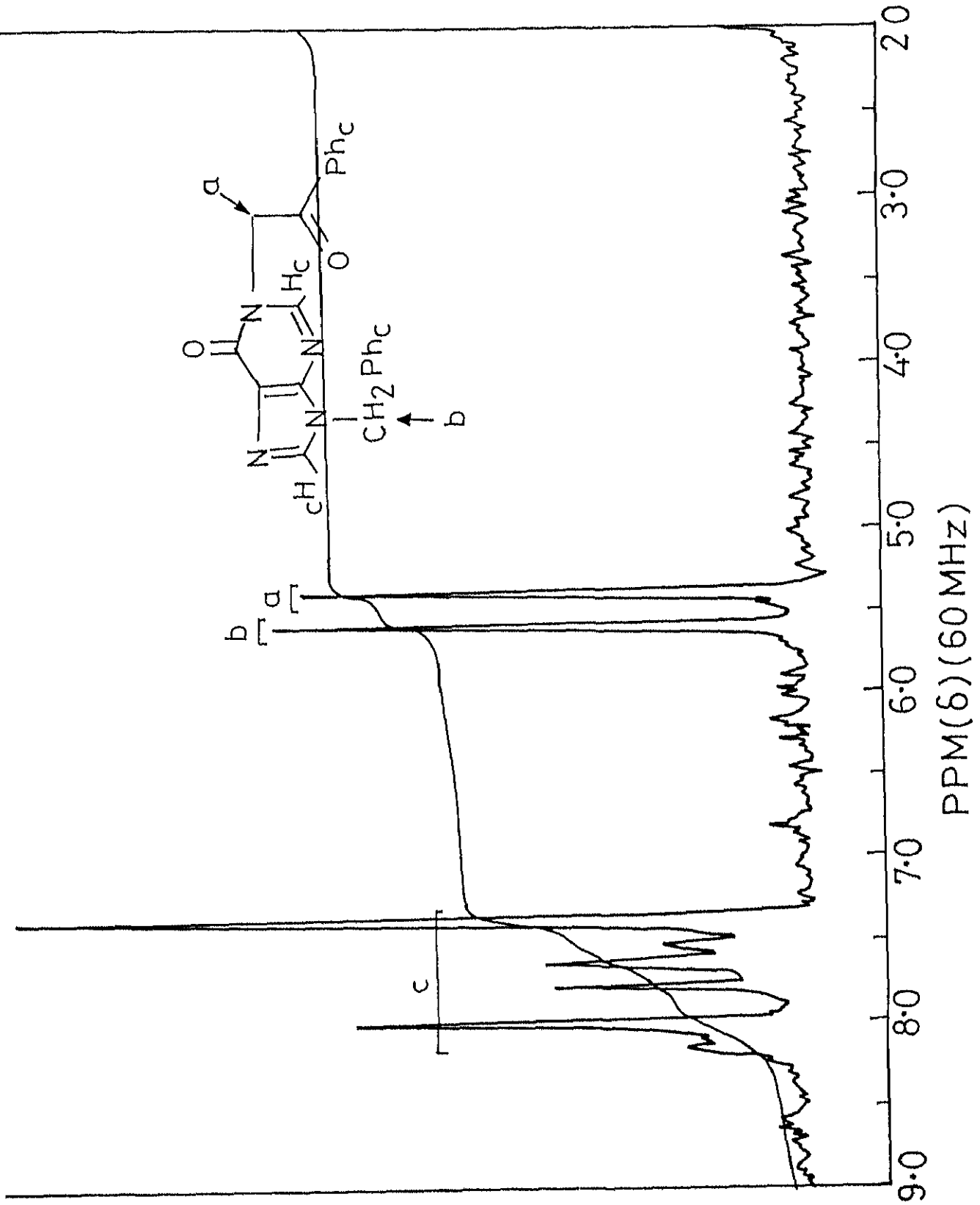

O
a
NH—CH2—Ph
NH2
b
a
b
9·0
8·0
7·0
6·0
5·0
4·0
PPM(δ) (60MHz)

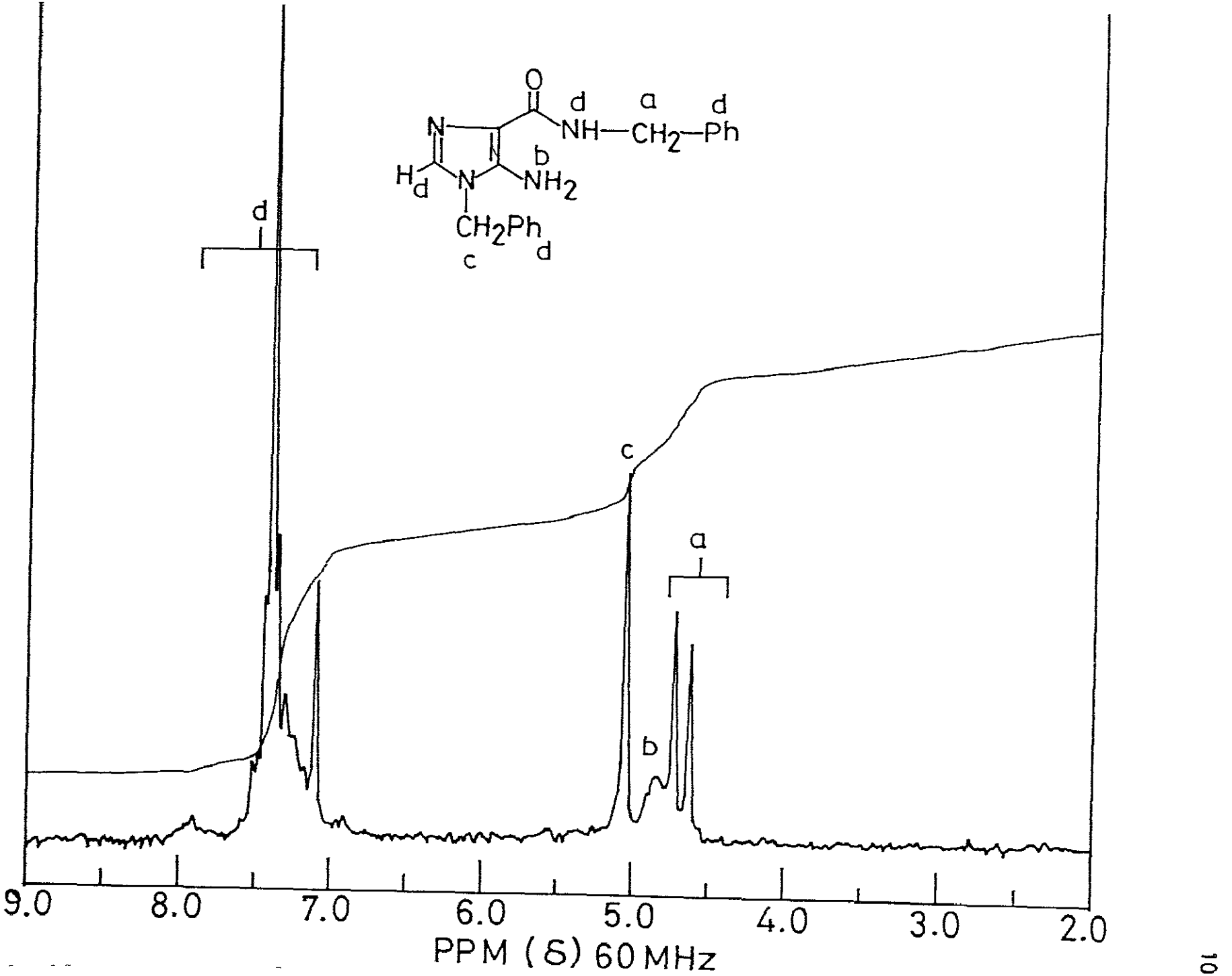

a
c
b
N
Hc
Hc
N
Phc
CH2—(CH2)16—CH3
b
a
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

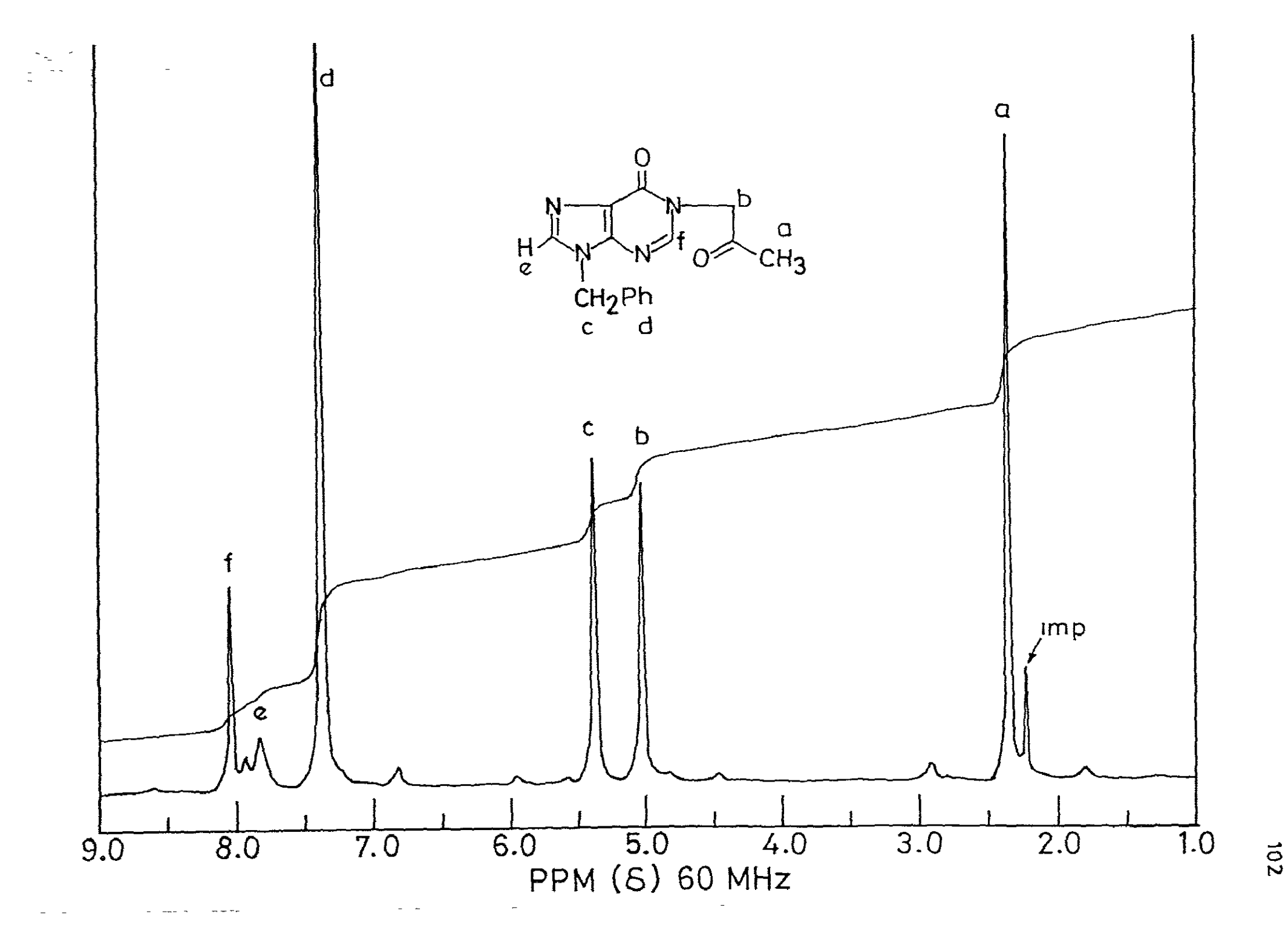

a
N
H_d
b
H_e
N
CH_3
$CH_2-(CH_2)_{16}-CH_3$
c
a
$CHCl_3$
e
d
c
b
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60MHz

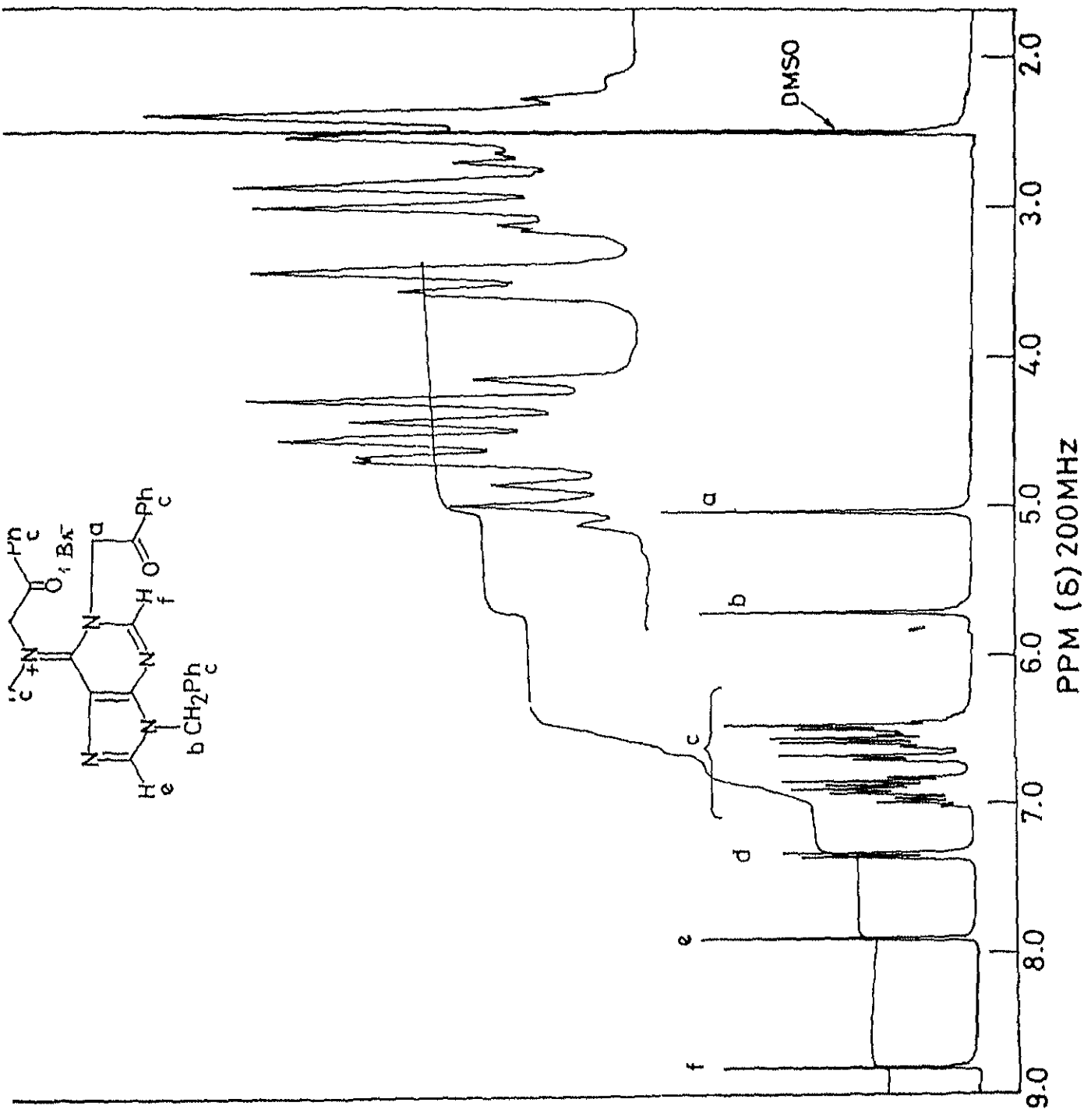

He
O
e
H
d
NH—CH2-(CH2)16—CH3
b
a
H
e
NH2
c
Hd
a
e
d
c
b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

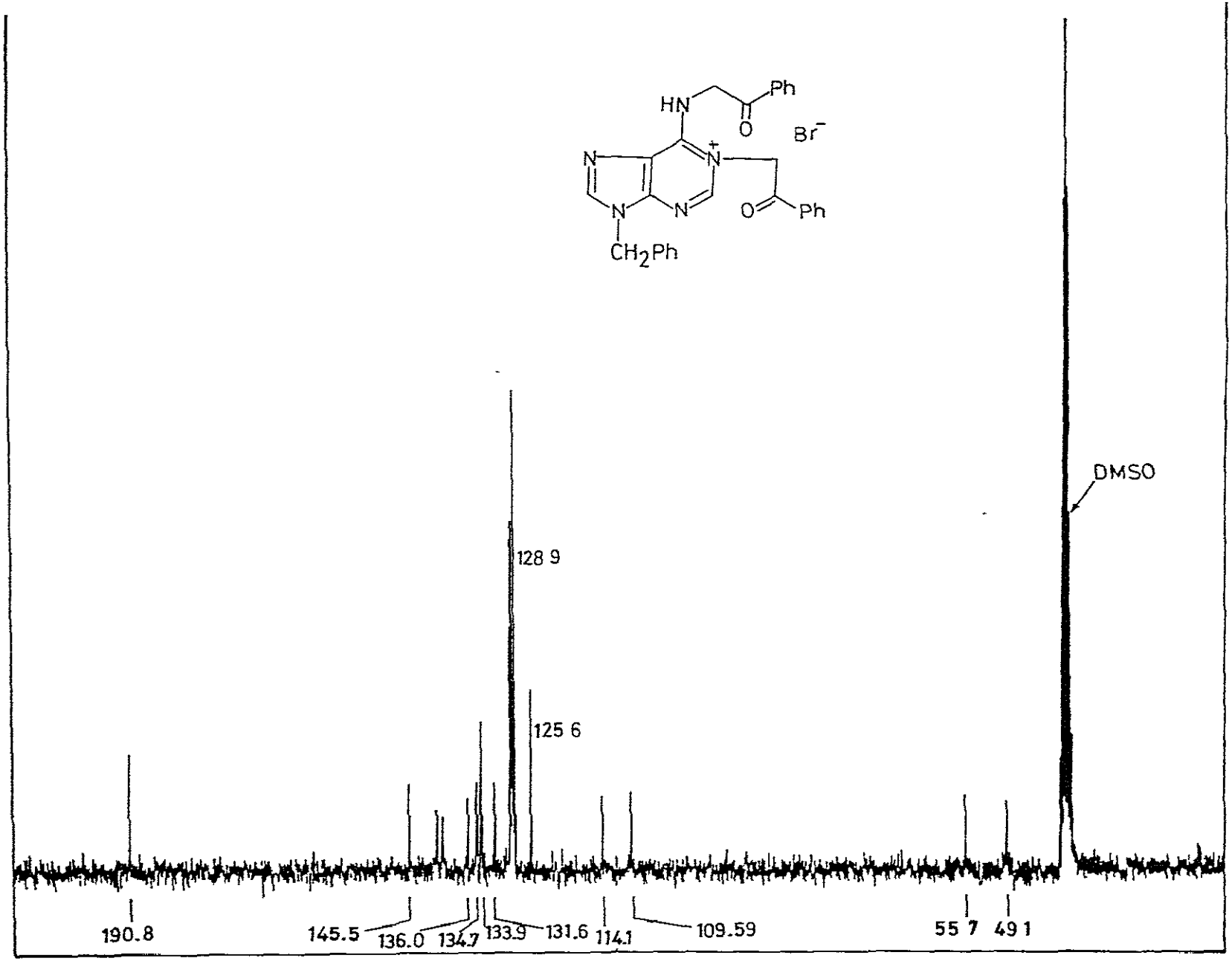

N
Hc
Hc
N
Ph
c
H b
a
a
a
a
a
c
a
b
.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

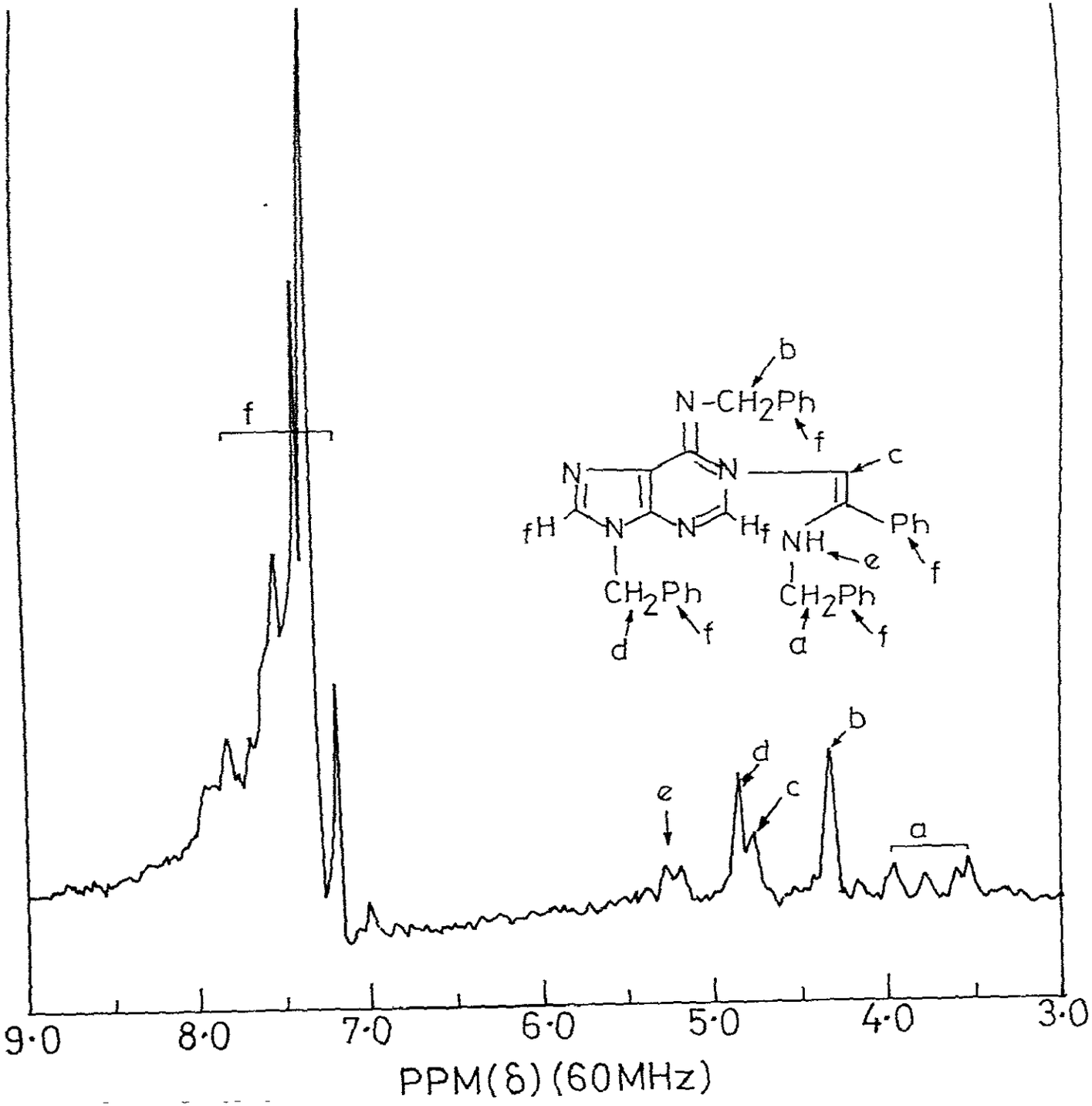

a
Phc
O
Hc
N
O
N
N
cH
N
CH2 Phc
b
a
b
c
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
PPM(δ)(60 MHz)

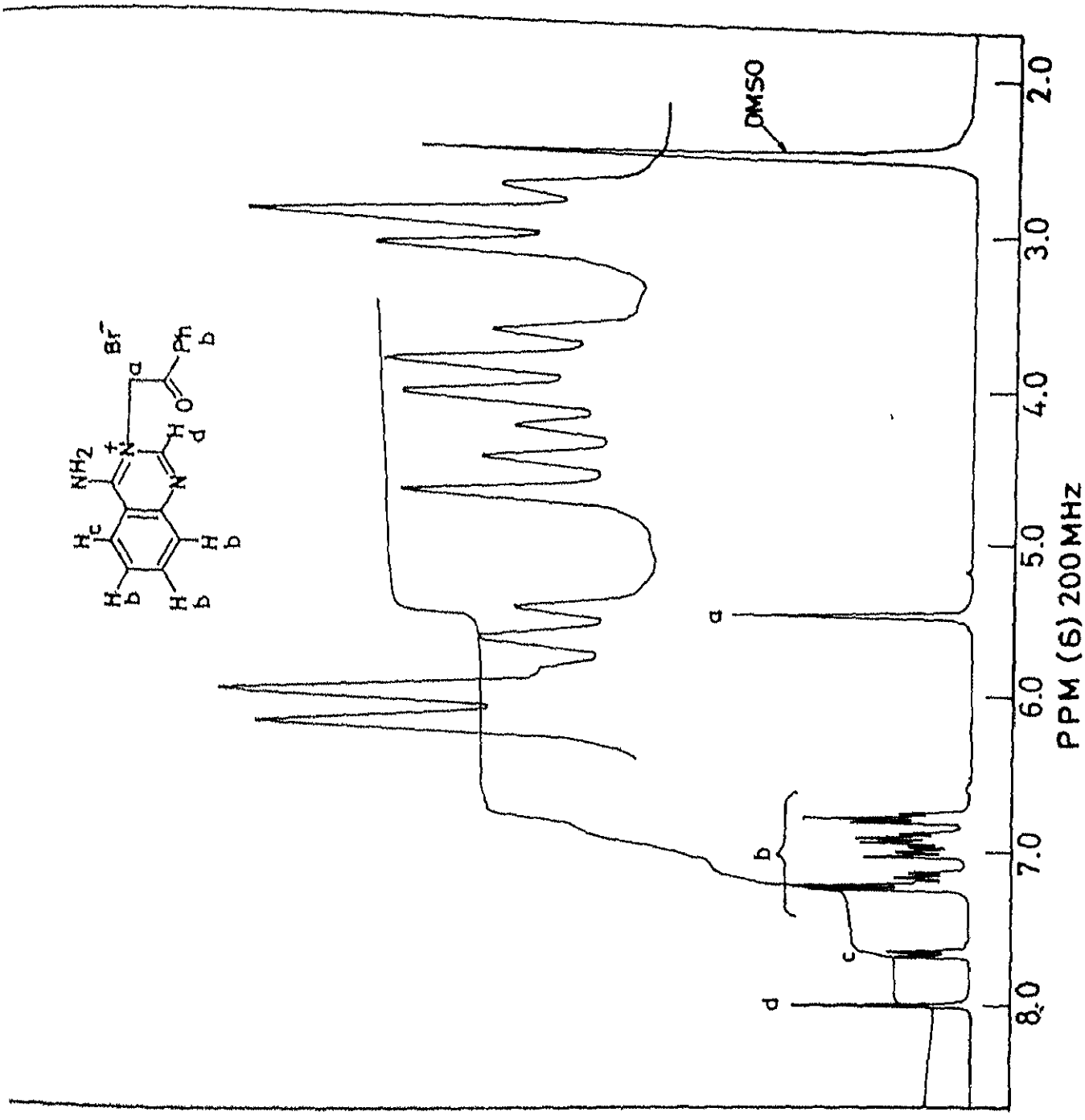

O
d
a
d
NH—CH2—Ph
N
b
NH2
Hd
N
CH2Ph
c
d
d
c
a
b
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz

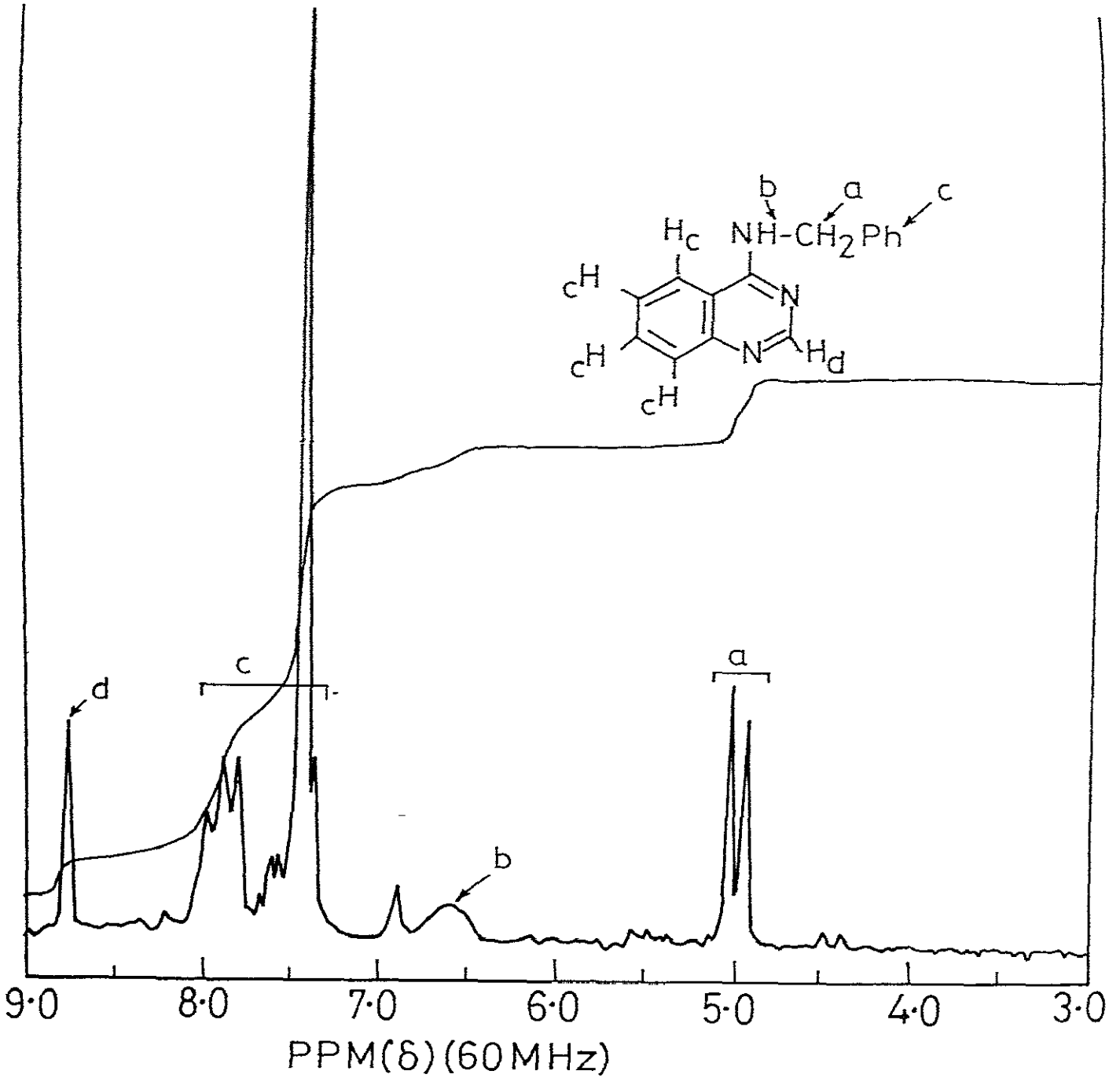

d
a
O
N
N
b
a
H
e
N
N
f
O
CH3
CH2Ph
c
d
c
b
f
e
imp
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

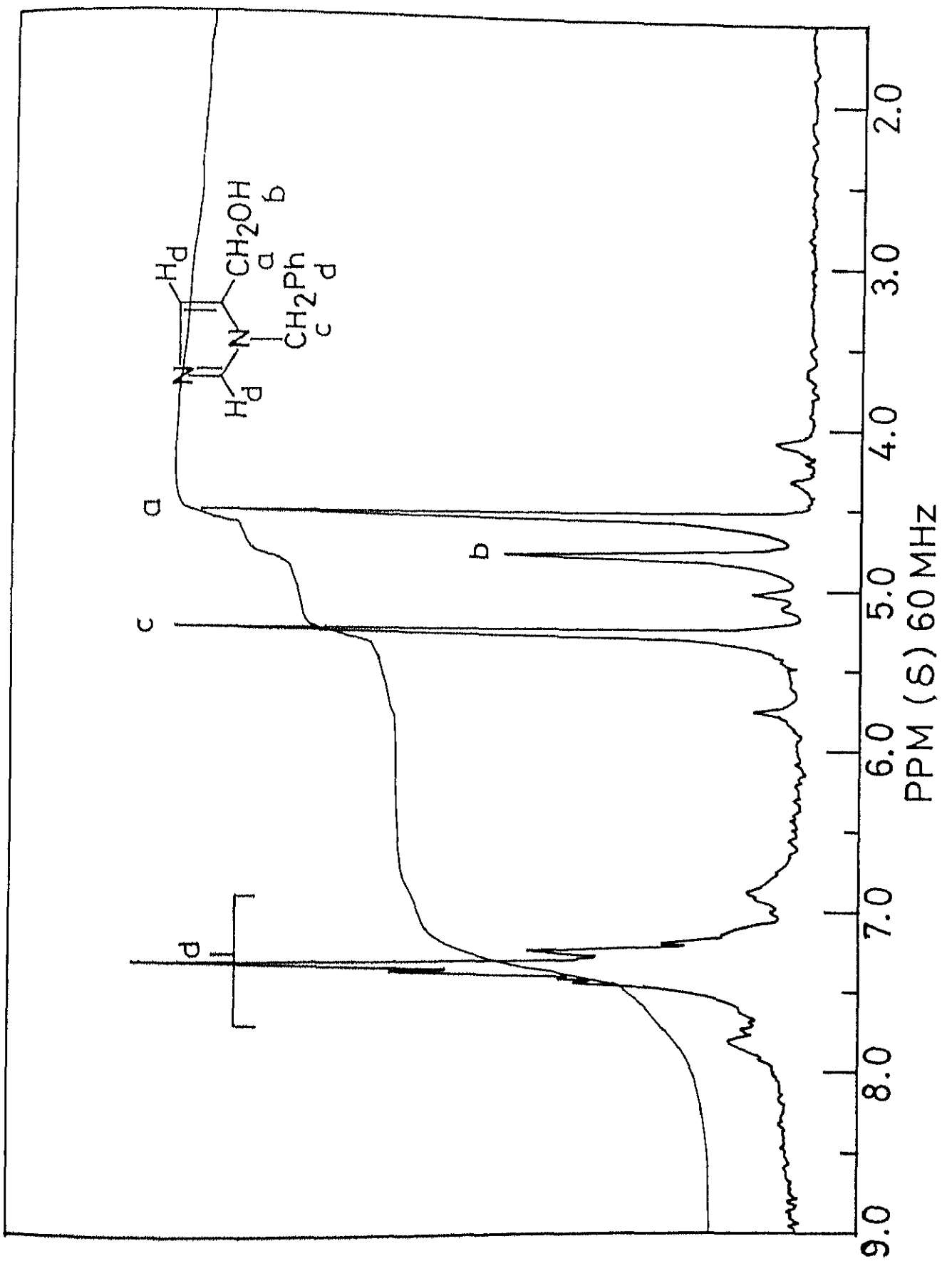

DMSO
PPM (δ) 200MHz
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
a
b
c
d
e
f
Ph
Br⁻
CH2Ph

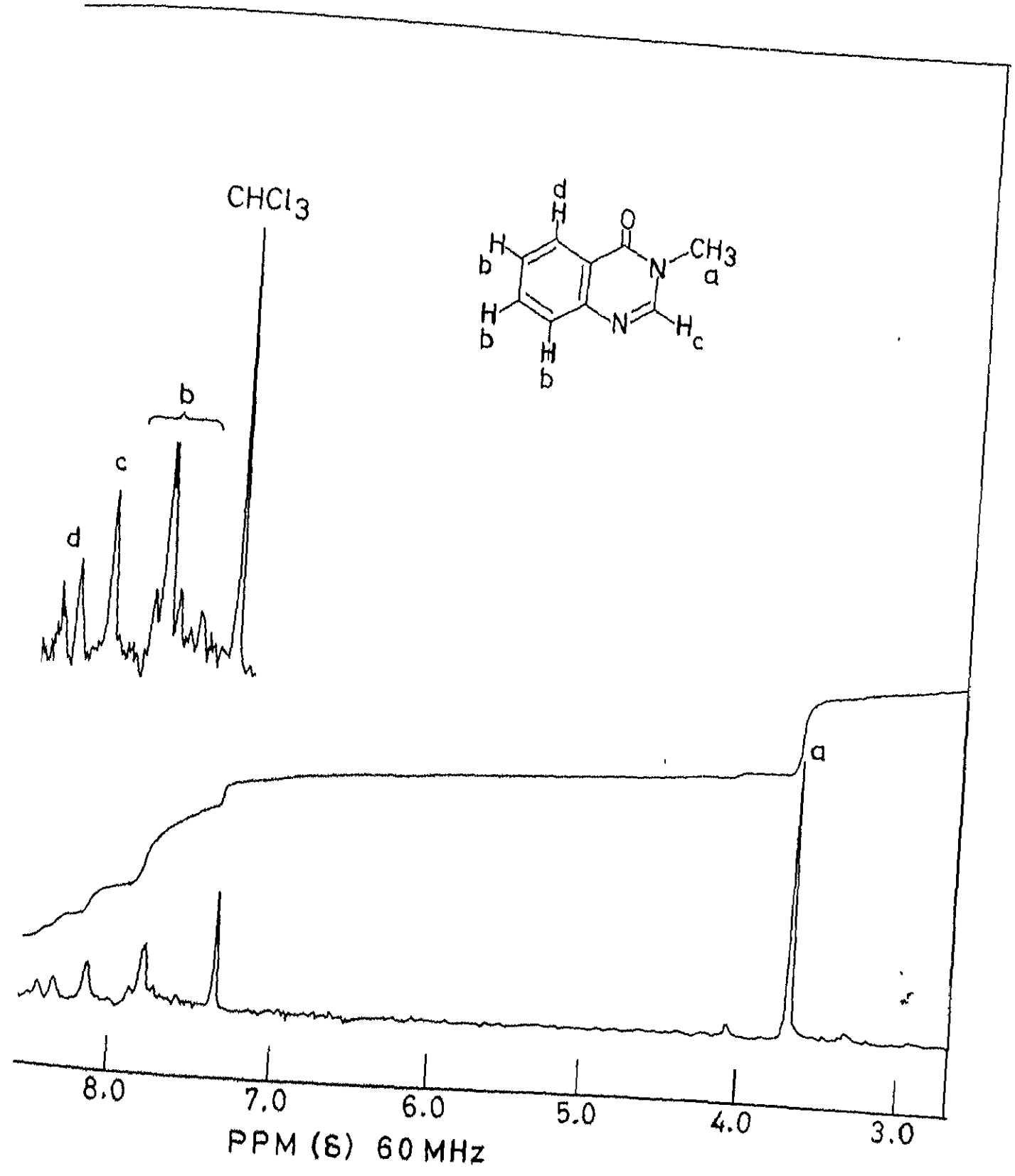

HN
Ph
O
Br⁻
N
N
N
N
O
Ph
CH2Ph
DMSO
128 9
125 6
190.8
145.5
136.0
134.7
133.9
131.6
114.1
109.59
55 7
49 1

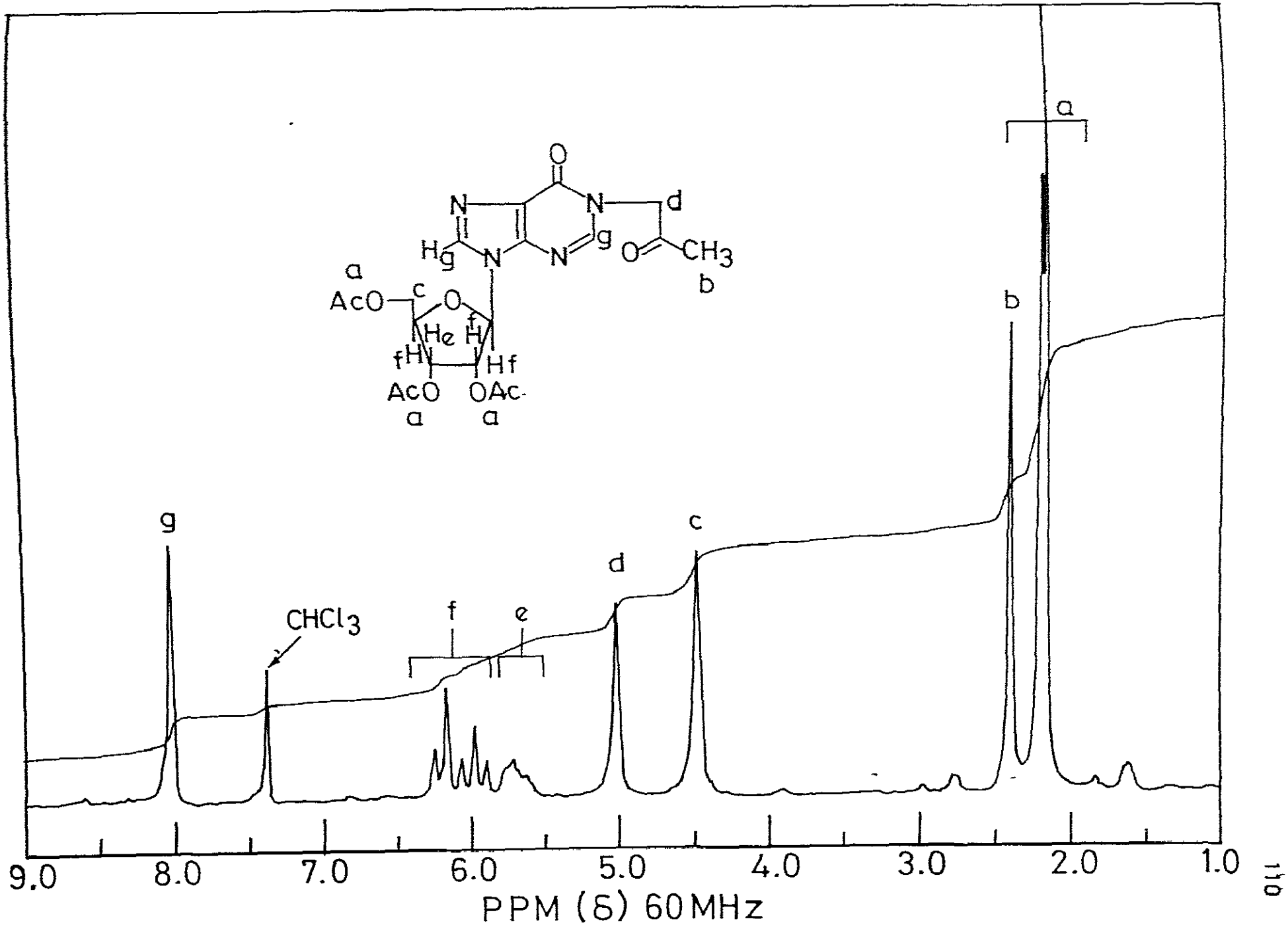

f
b
N-CH2Ph
f
c
N
N
fH
N
N
Hf
Ph
NH
e
f
CH2Ph
f
d
CH2Ph
f
a
b
d
c
e
a
9·0
8·0
7·0
6·0
5·0
4·0
3·0
PPM(δ)(60MHz)

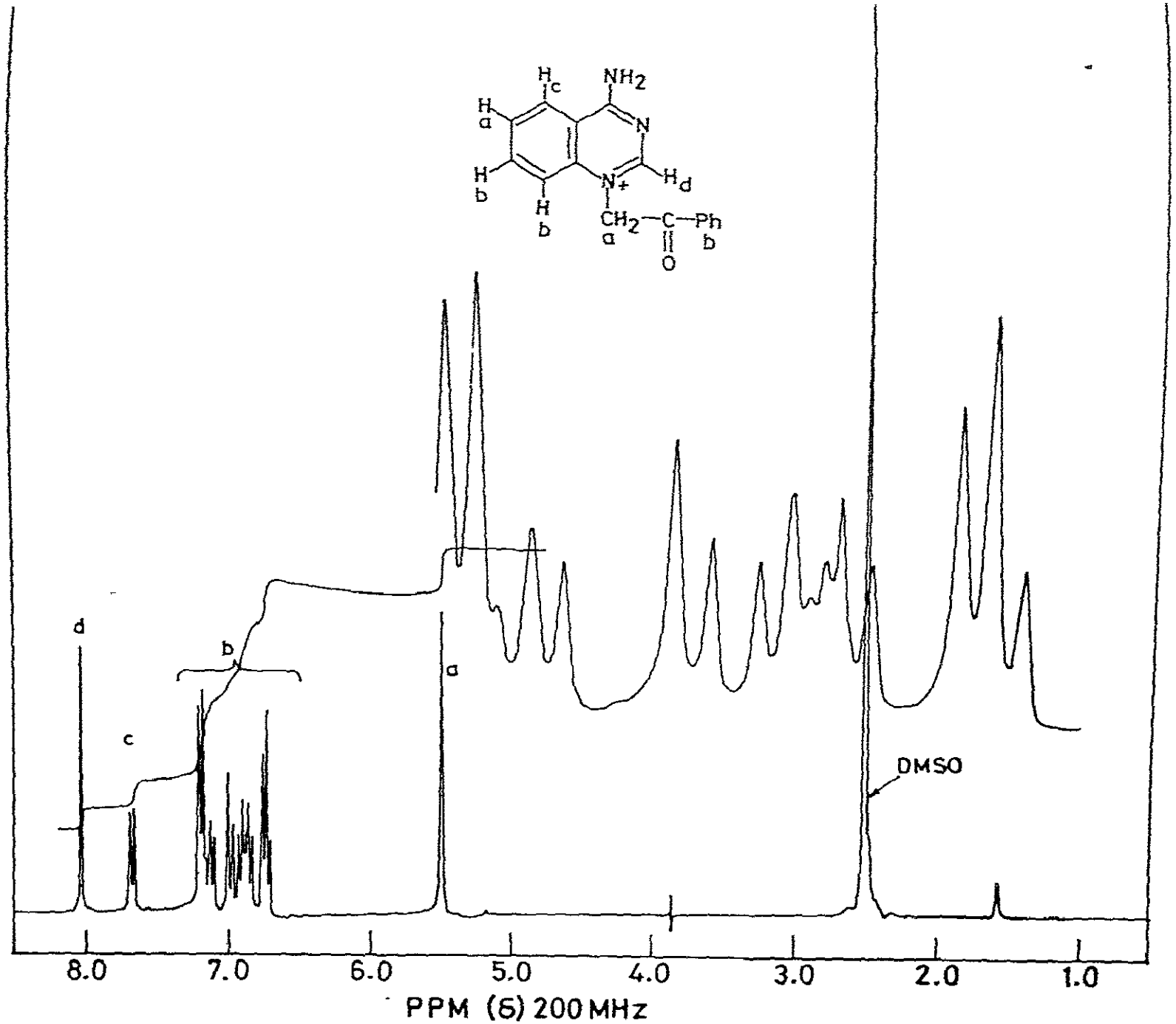

DMSO
a
b
c
d
2.0
3.0
4.0
5.0
6.0
7.0
8.0
PPM (δ) 200 MHz
Br⁻
NH2
N+
O
Ph
H

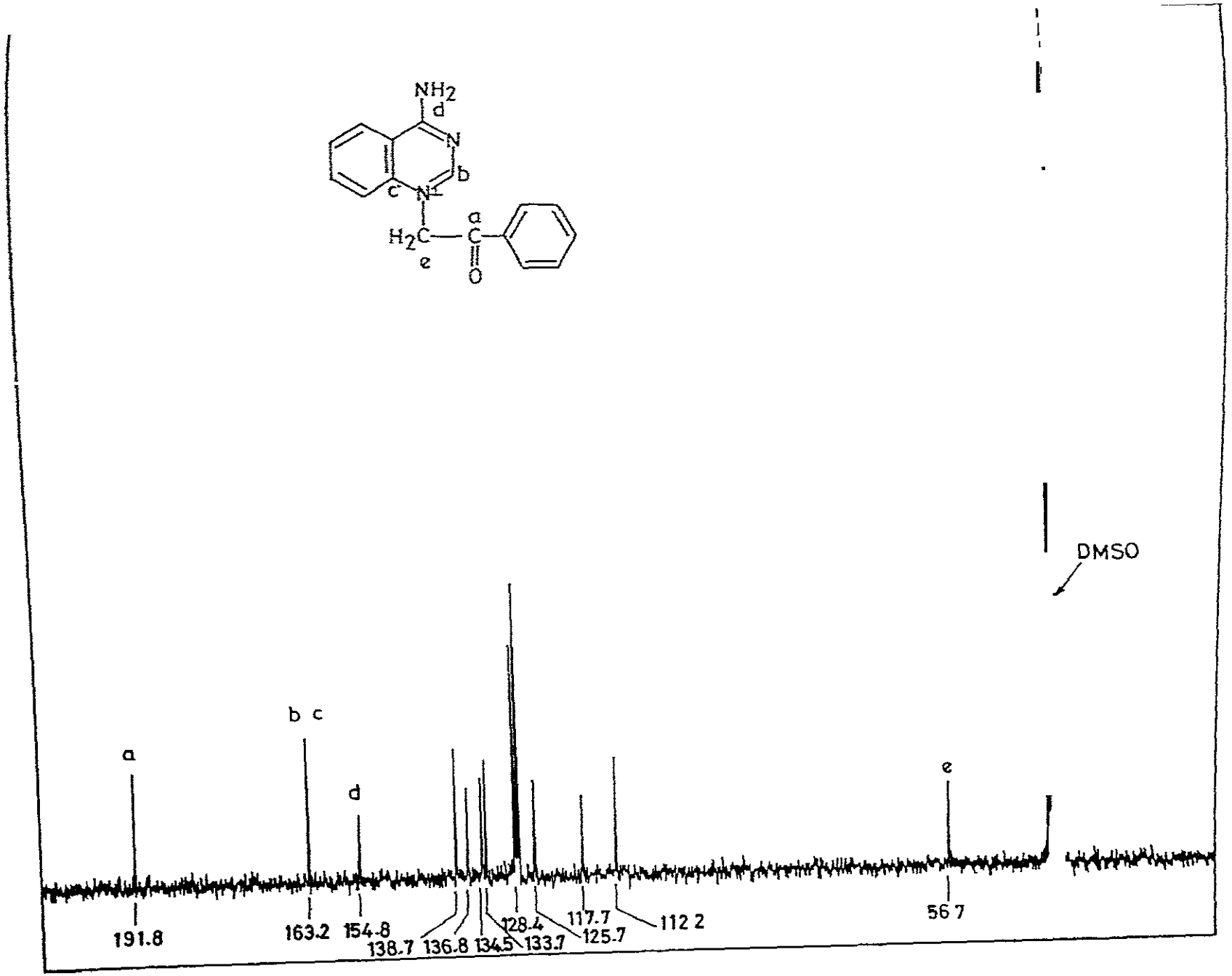

b
a
c
NH-CH2Ph
Hc
cH
cH
cH
N
N
Hd
d
c
a
b
9·0
8·0
7·0
6·0
5·0
4·0
3·0
PPM(δ)(60MHz)

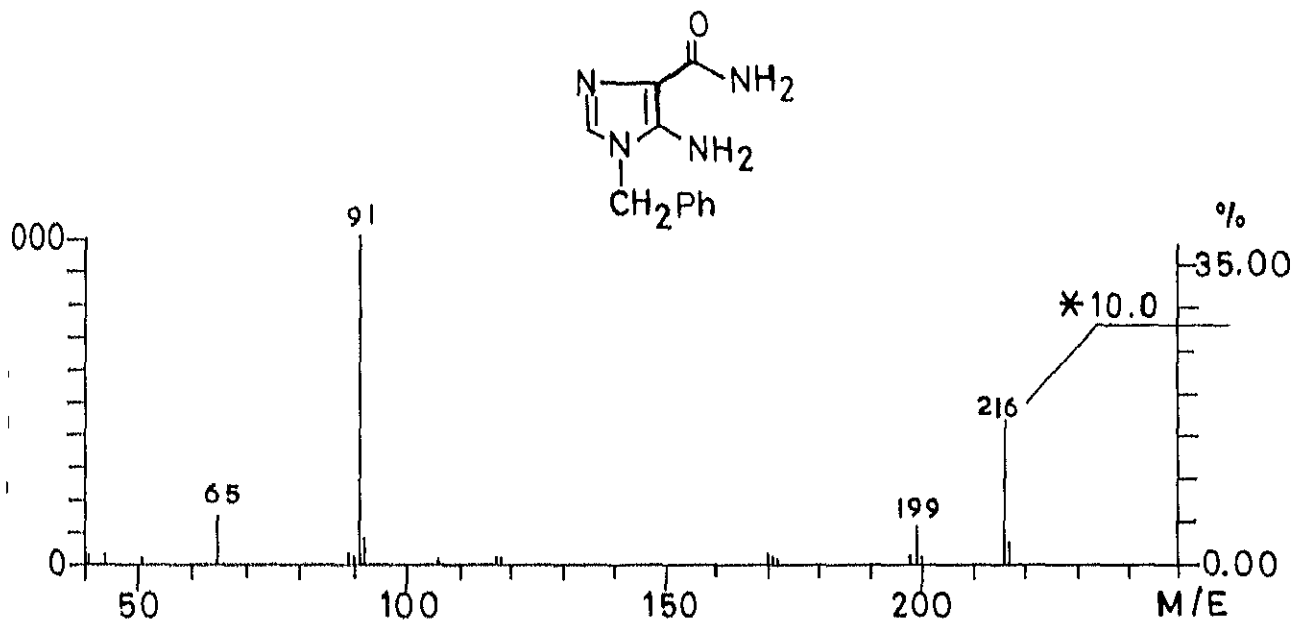

H_d
CH_2OH
a
b
CH_2Ph
c
d
H_d
N
N
a
b
c
d
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz

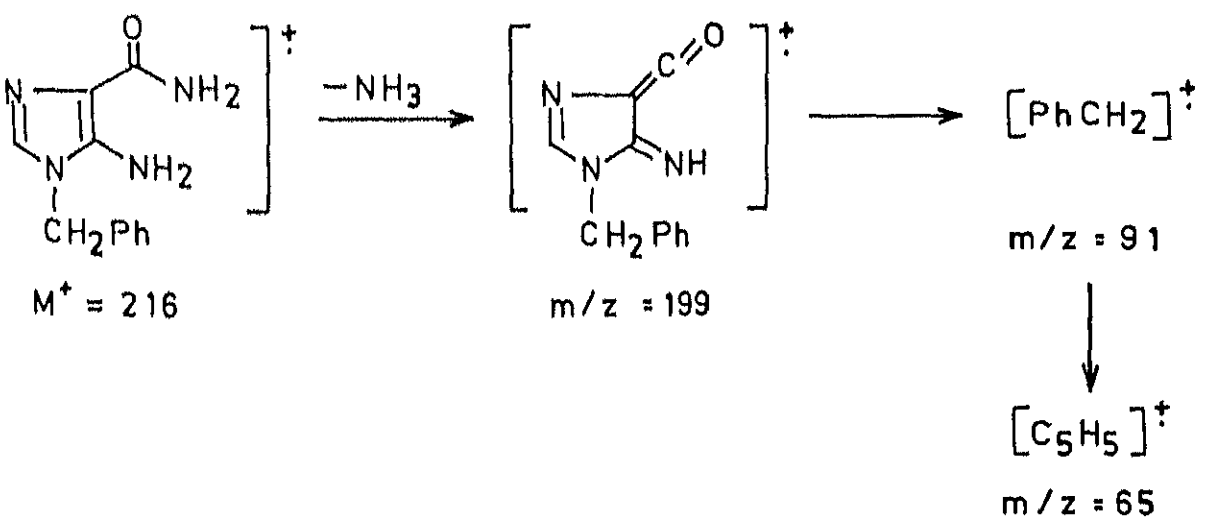

CHCl3
d
c
b
a
8.0
7.0
6.0
5.0
4.0
3.0
PPM (δ) 60 MHz

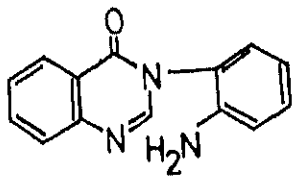

a
b
g
CHCl3
f
e
d
c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60MHz
110

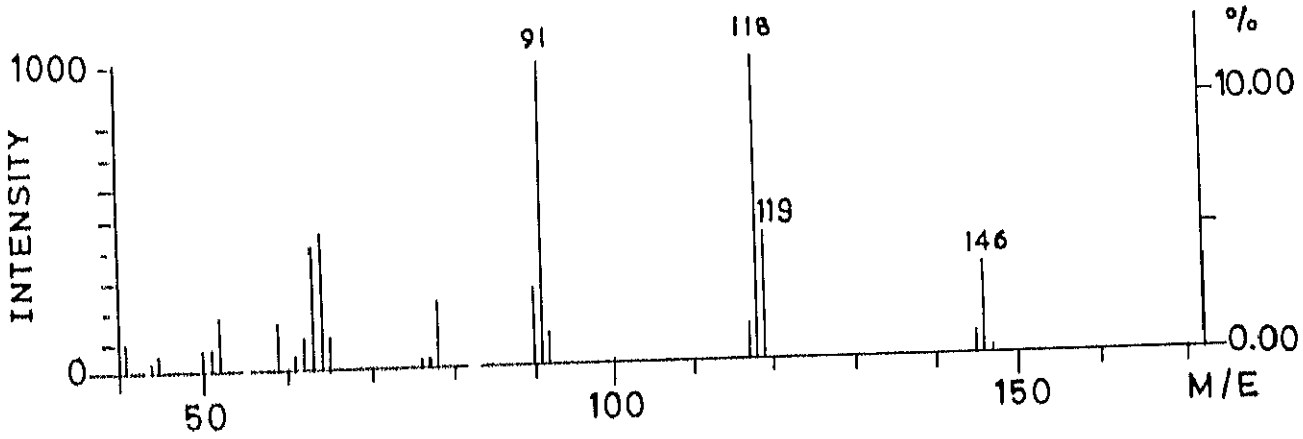

NH2
N
N+
Hc
Ha
Hb
Hb
Hd
CH2
C
Ph
O
a
b
b
d
c
a
DMSO
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 200 MHz

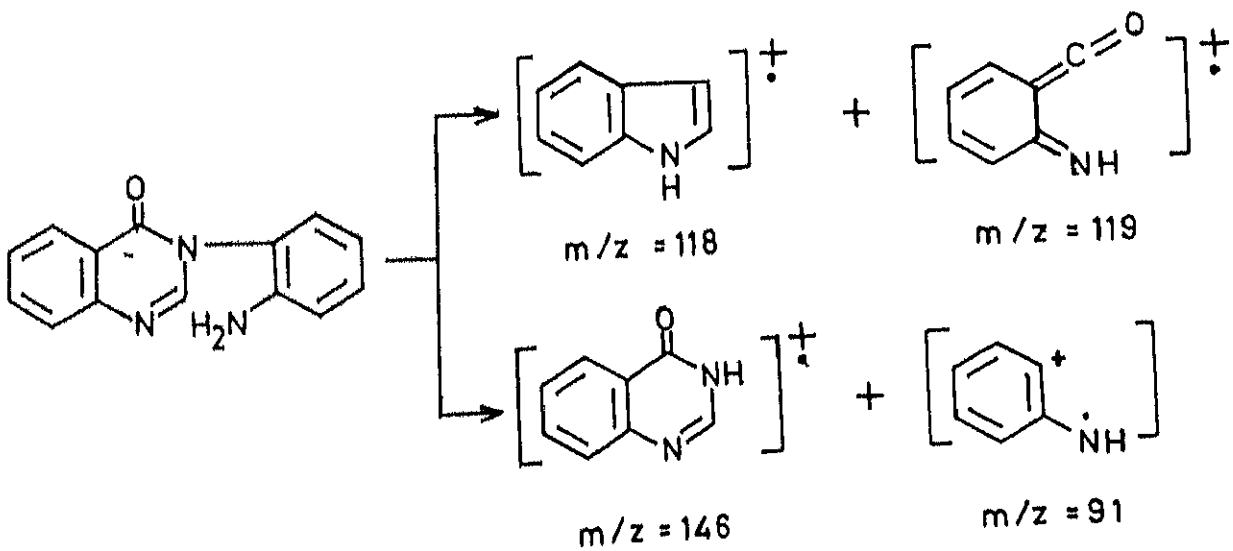

NH2
d
N
b
c
N+
a
H2C
C
e
O
DMSO
a
b c
d
e
191.8
163.2
154.8
138.7
136.8
134.5
128.4
133.7
117.7
125.7
112 2
56 7

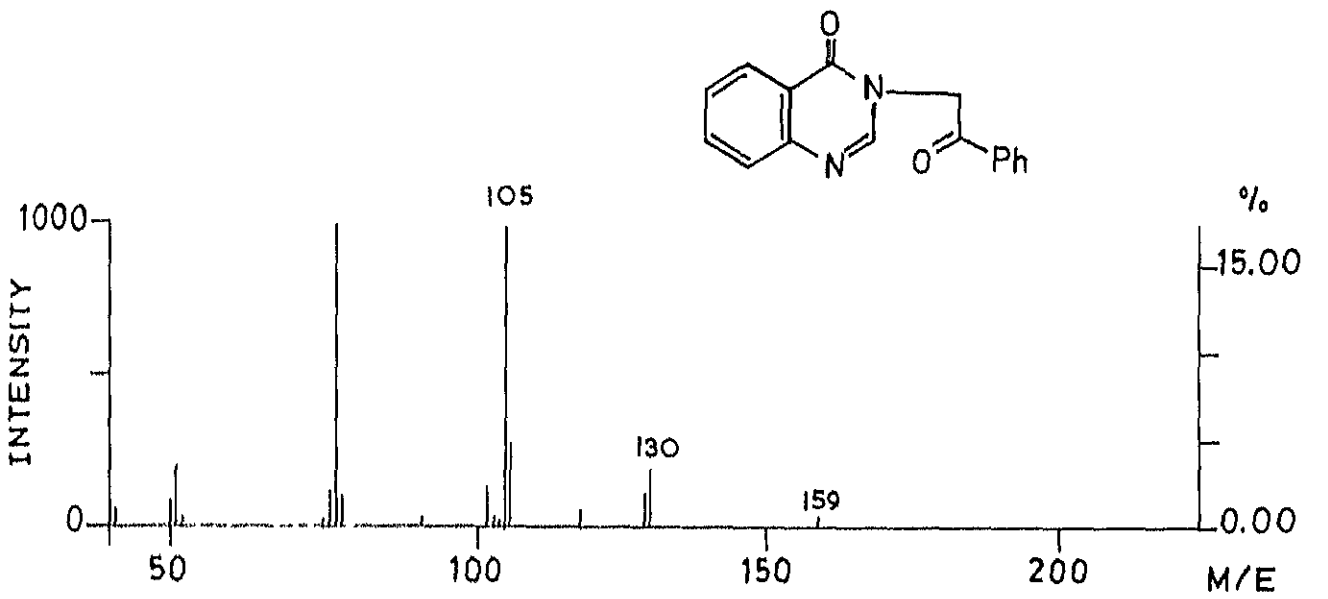

000
0
91
65
199
216
*10.0
%
35.00
0.00
50
100
150
200
M/E

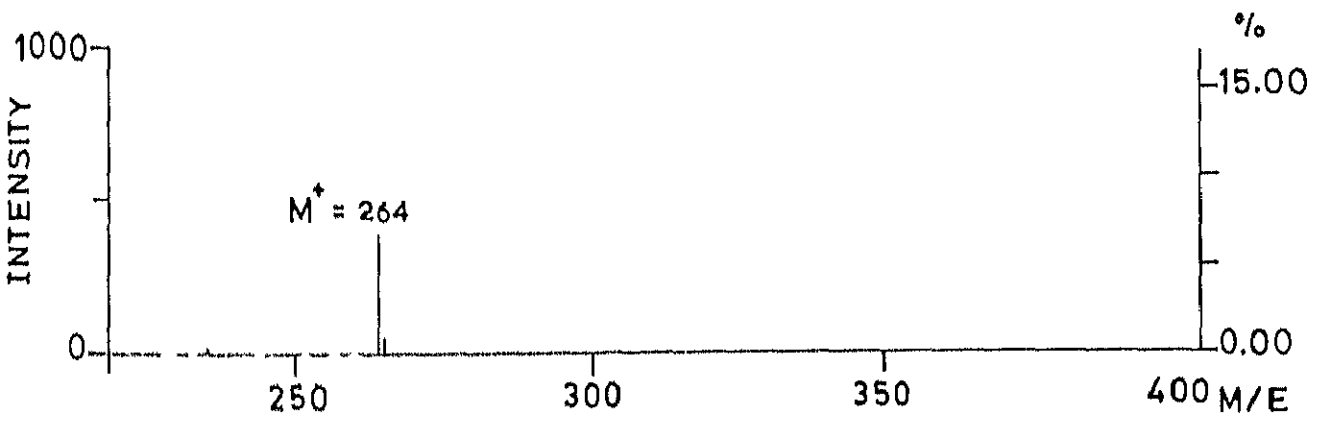

−NH3
CH2Ph
M+ = 216
m/z = 199
[PhCH2]+
m/z = 91
[C5H5]+
m/z = 65

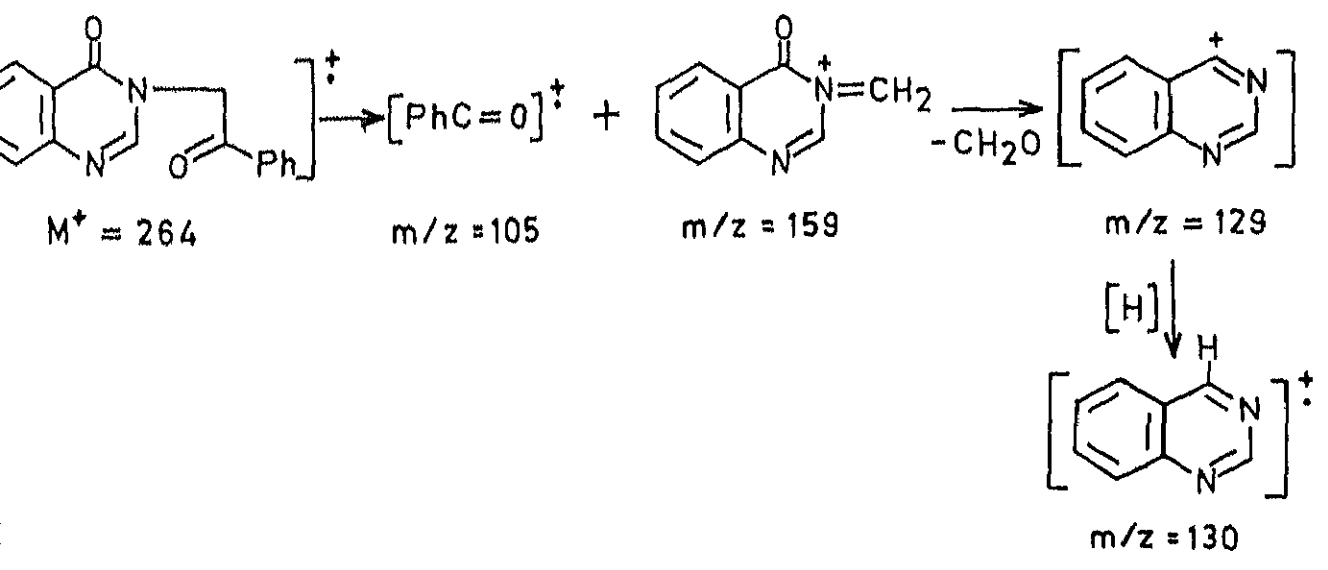


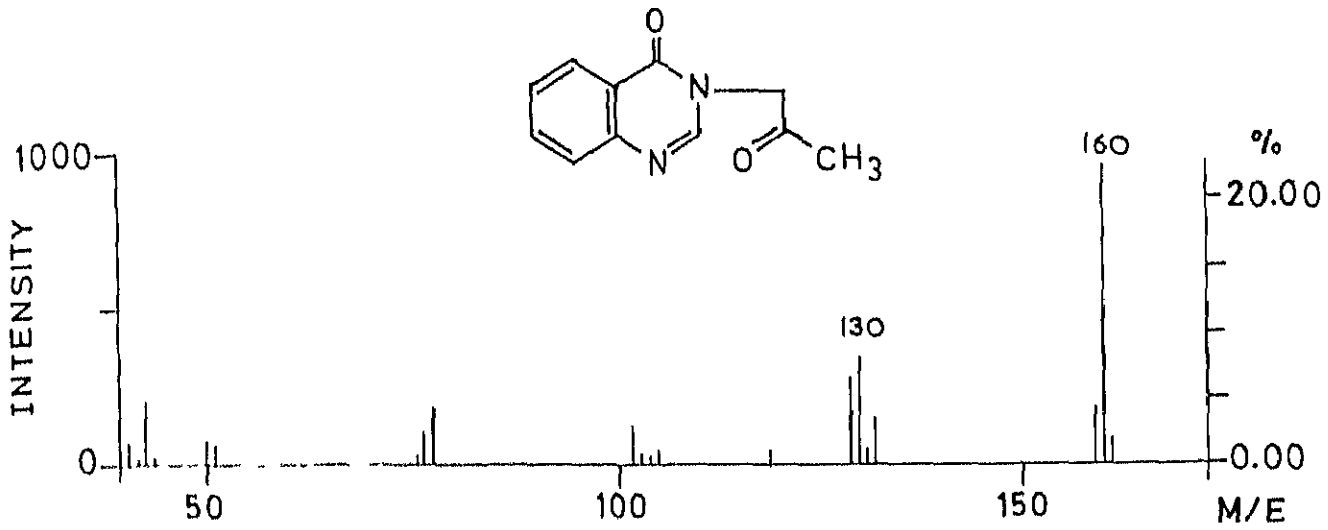

1000
0
INTENSITY
91
118
119
146
%
10.00
0.00
50
100
150
M/E

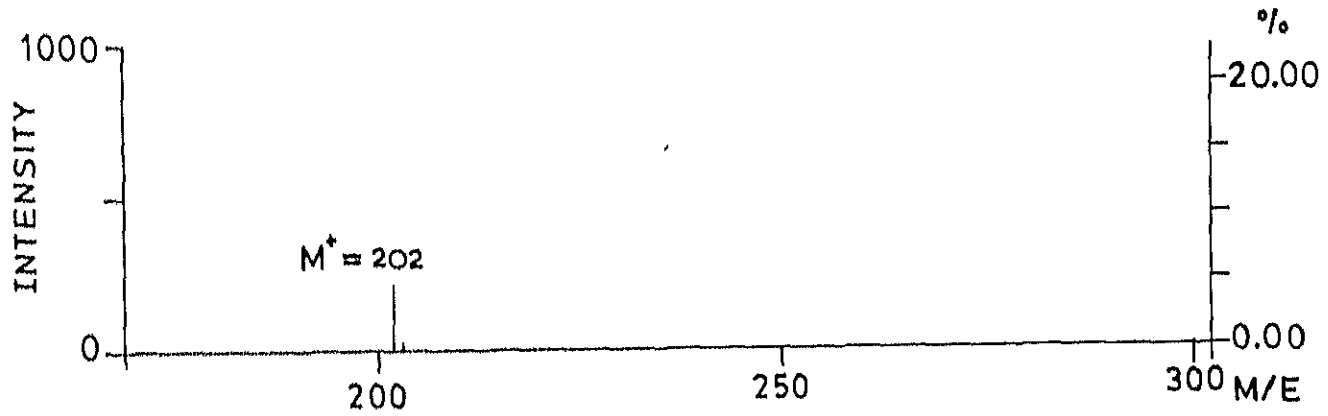

m/z = 118
m/z = 119
m/z = 146
m/z = 91

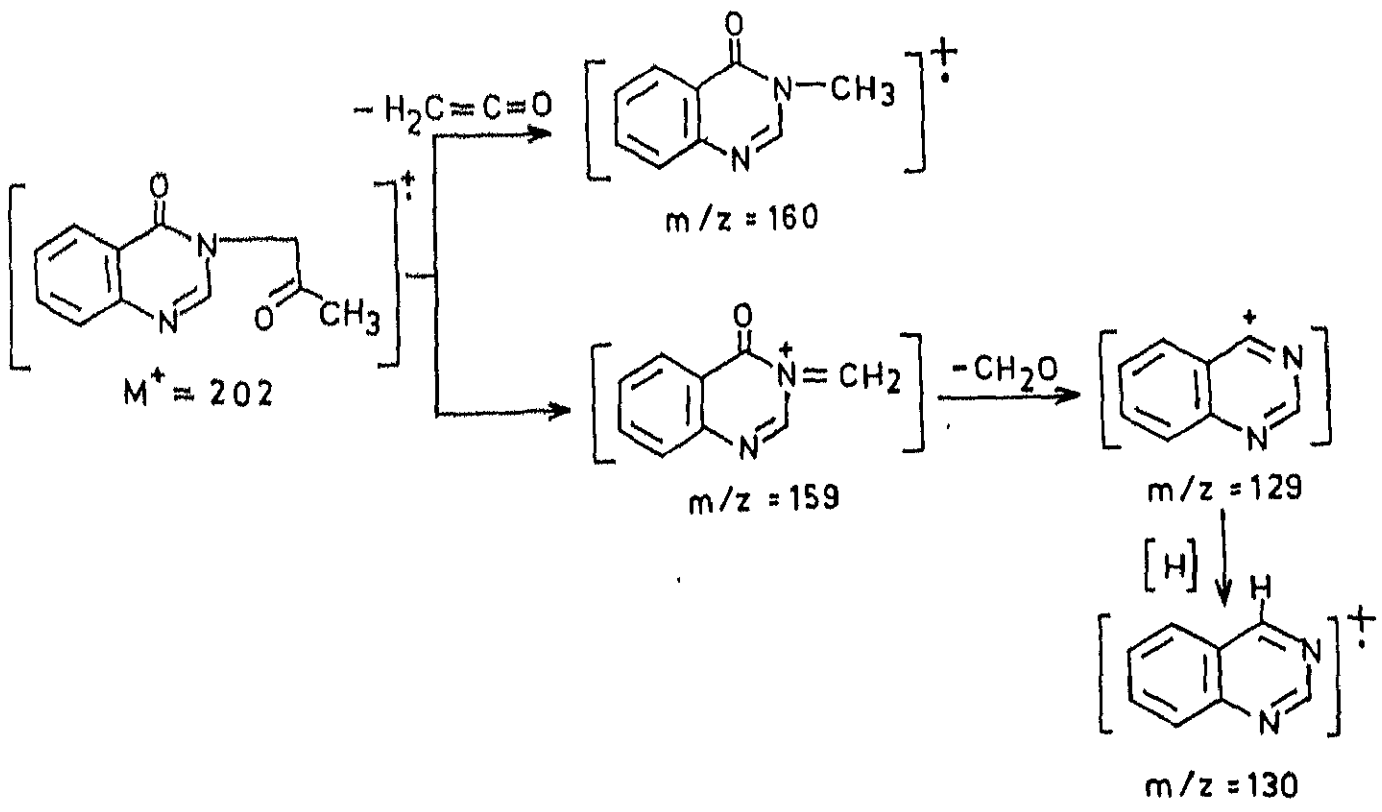

105
%
1000
15.00
INTENSITY
130
159
0
0.00
50
100
150
200
M/E

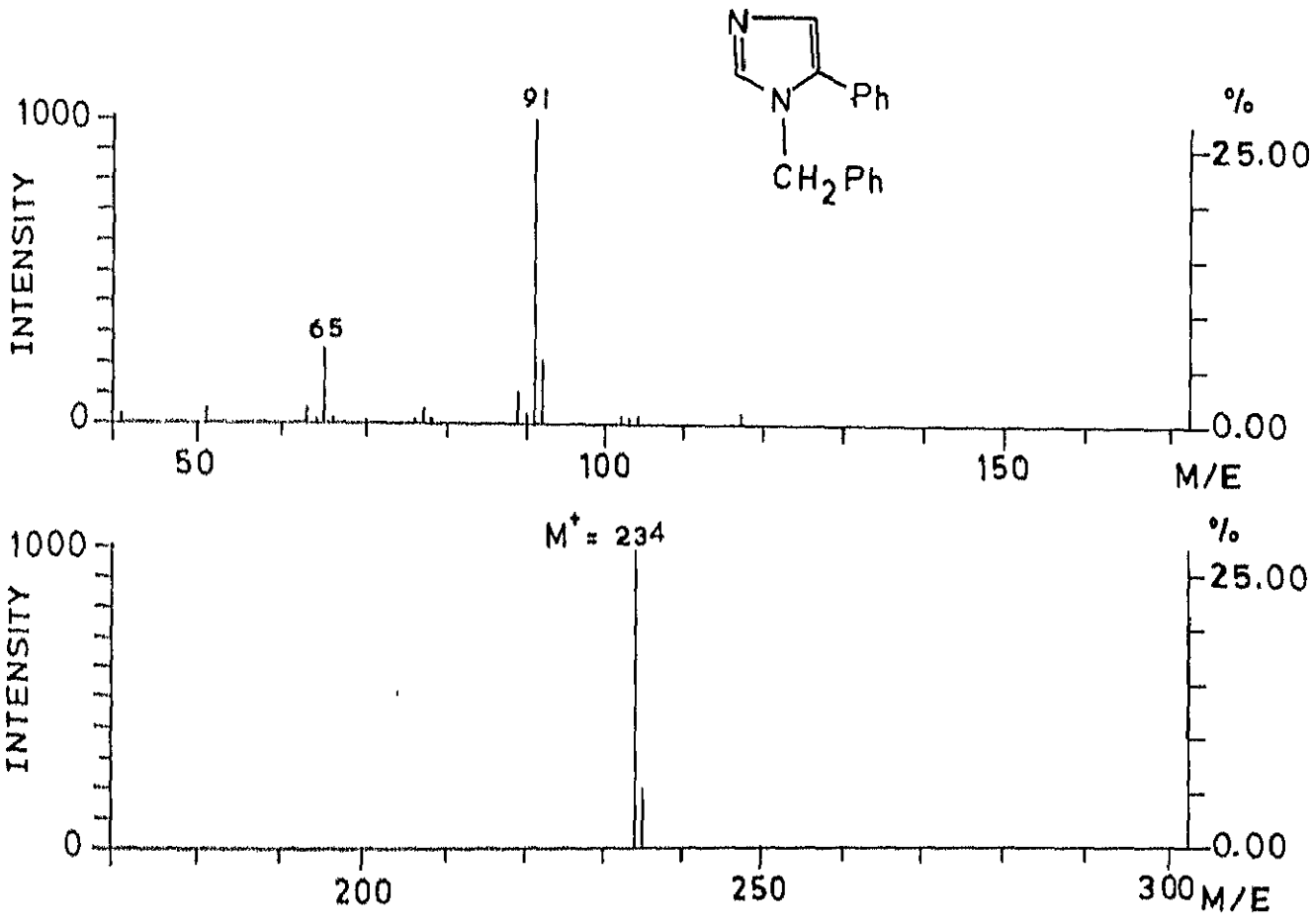

%
1000
15.00
INTENSITY
M+ = 264
0
0.00
250
300
350
400
M/E

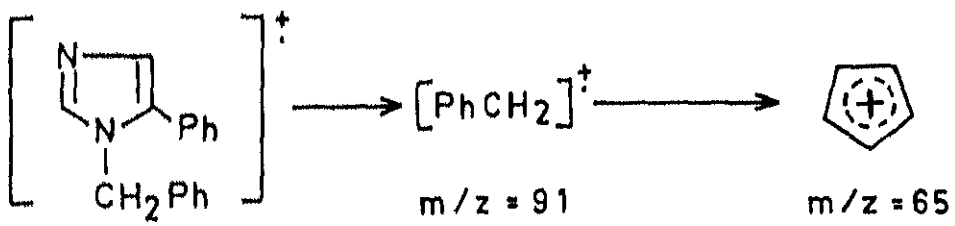

[PhC=O]+
+
-CH2O
M+ = 264
m/z = 105
m/z = 159
m/z = 129
[H]
m/z = 130


1000
INTENSITY
0
50
100
150
160
130
%
20.00
0.00
M/E

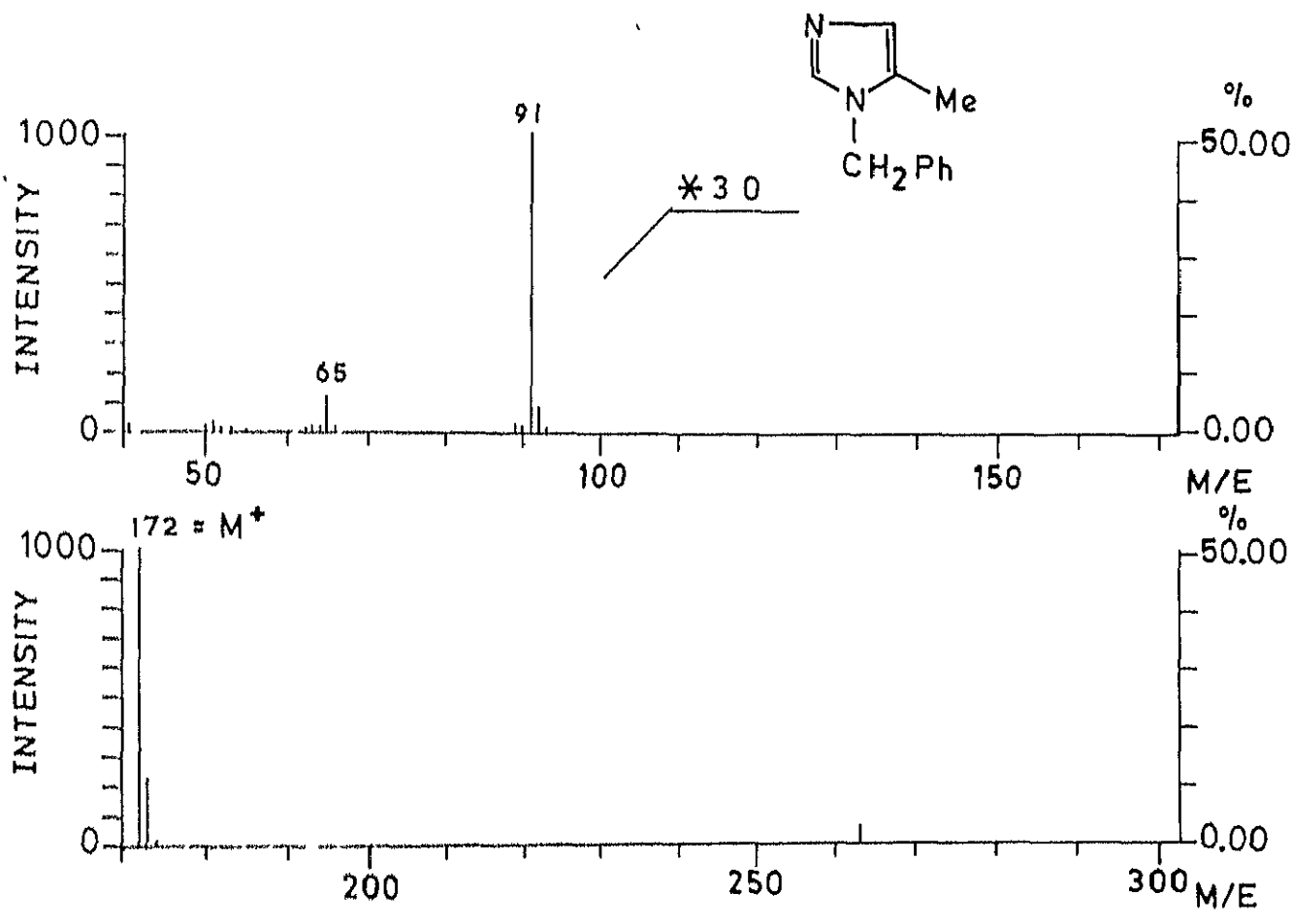

1000
INTENSITY
0
M⁺ = 202
200
250
300
%
20.00
0.00
M/E

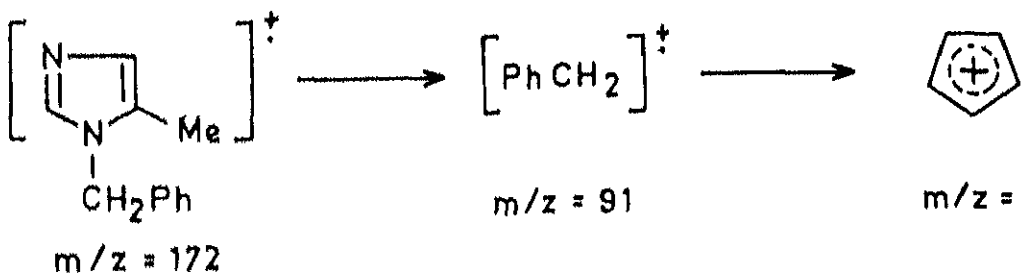

- H2C=C=O
M⁺ = 202
m/z = 160
m/z = 159
-CH2O
m/z = 129
[H]
m/z = 130


1000
INTENSITY
0
91
65
50
100
150
M/E
%
25.00
0.00
M+ = 234
200
250
300

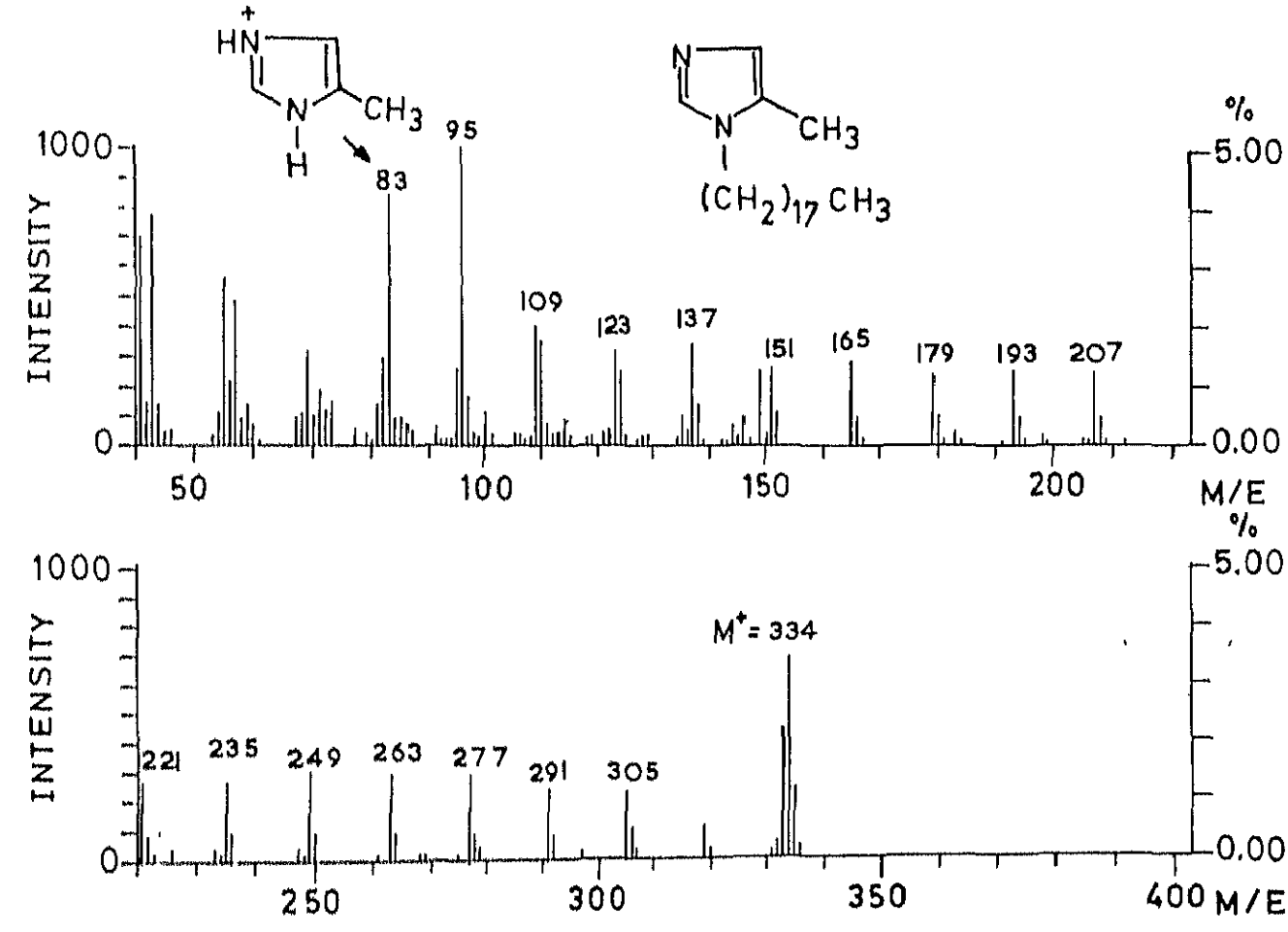

Ph
CH2Ph
[PhCH2]+
m/z = 91
m/z = 65

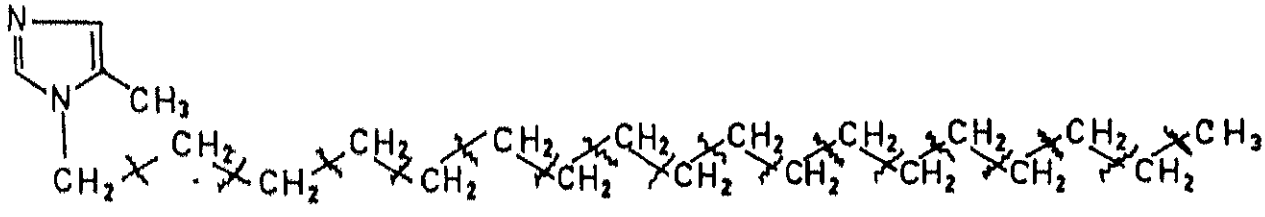
$M^+ = 234$

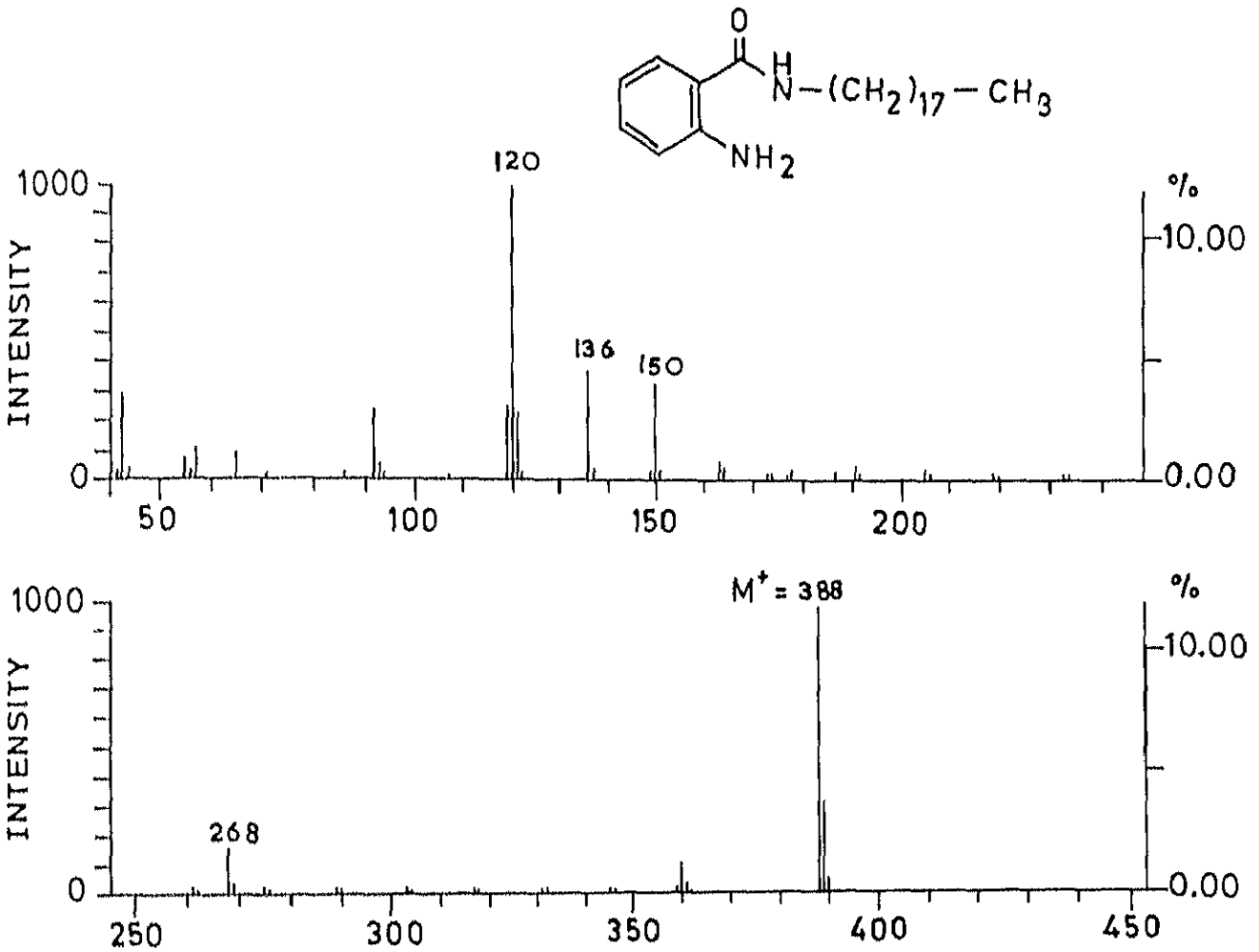


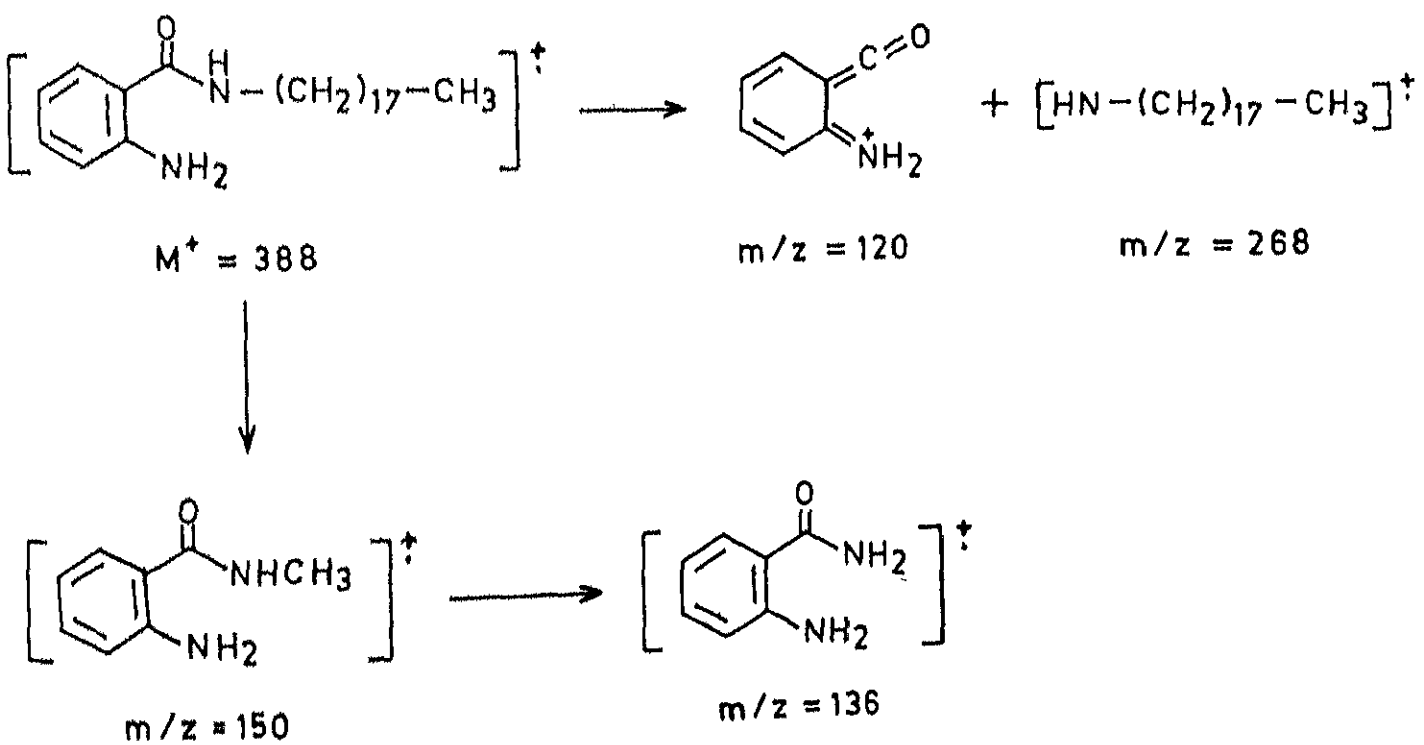


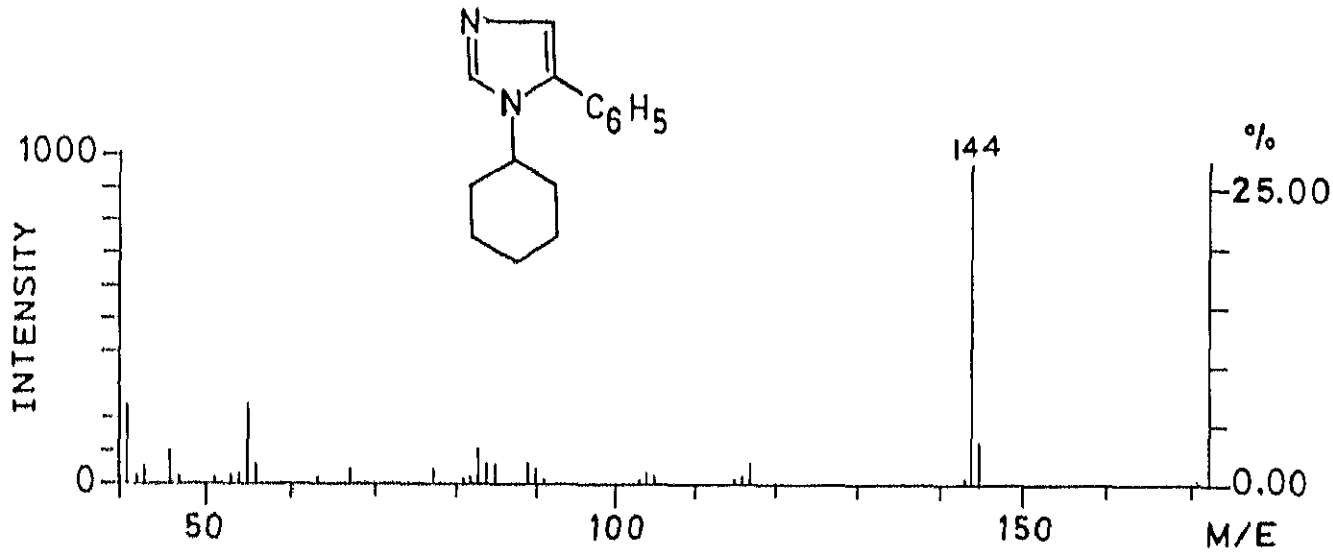
m/z = 172 m/z = 91 m/z = 65

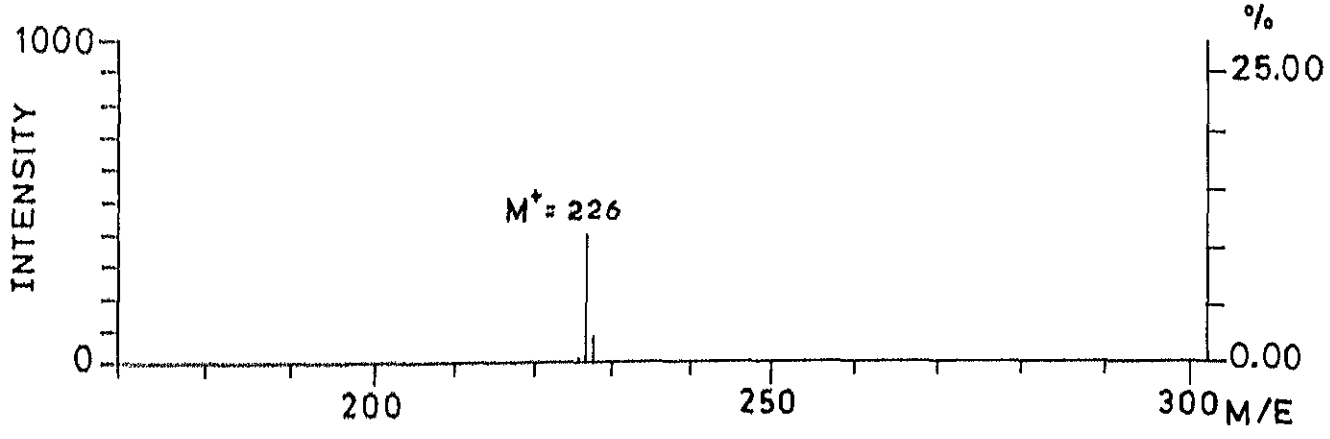

HN
CH3
N
H
83
95
N
CH3
(CH2)17 CH3
1000
INTENSITY
0
%
5.00
0.00
109
123
137
151
165
179
193
207
50
100
150
200
M/E
M+= 334
221
235
249
263
277
291
305
250
300
350
400

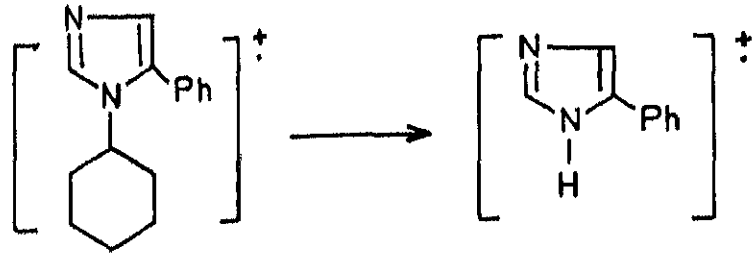

N
CH3
CH2
CH3


INTENSITY
1000
0
120
136
150
50
100
150
200
%
10.00
0.00
M+ = 388
268
250
300
350
400
450

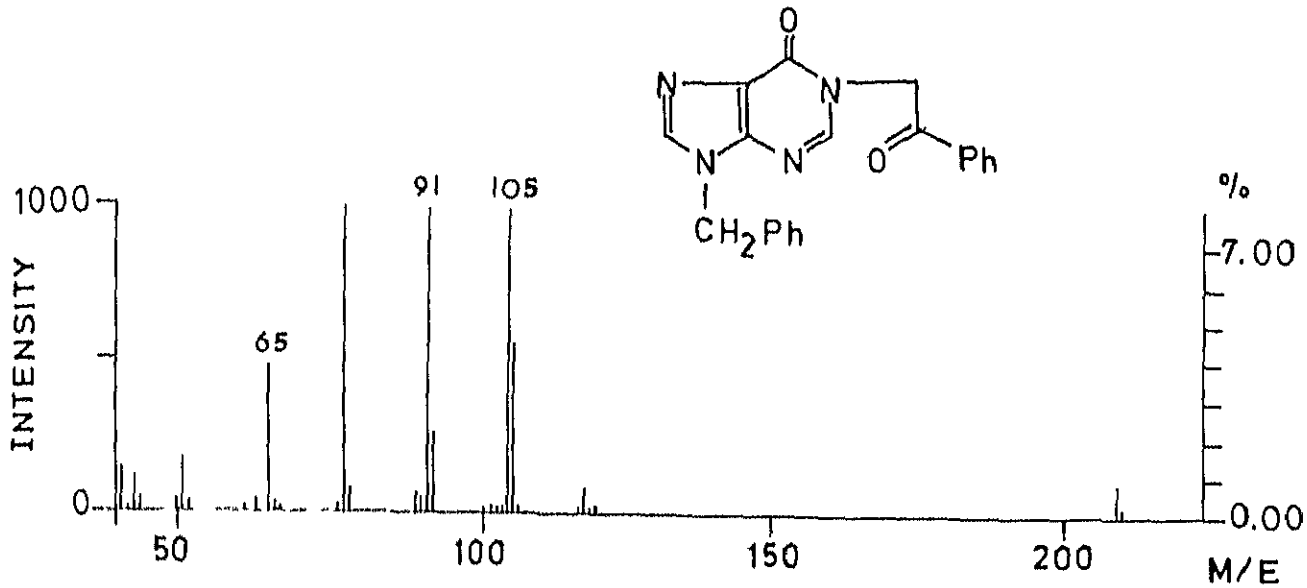

M+ = 388
m/z = 120
m/z = 268
m/z = 150
m/z = 136

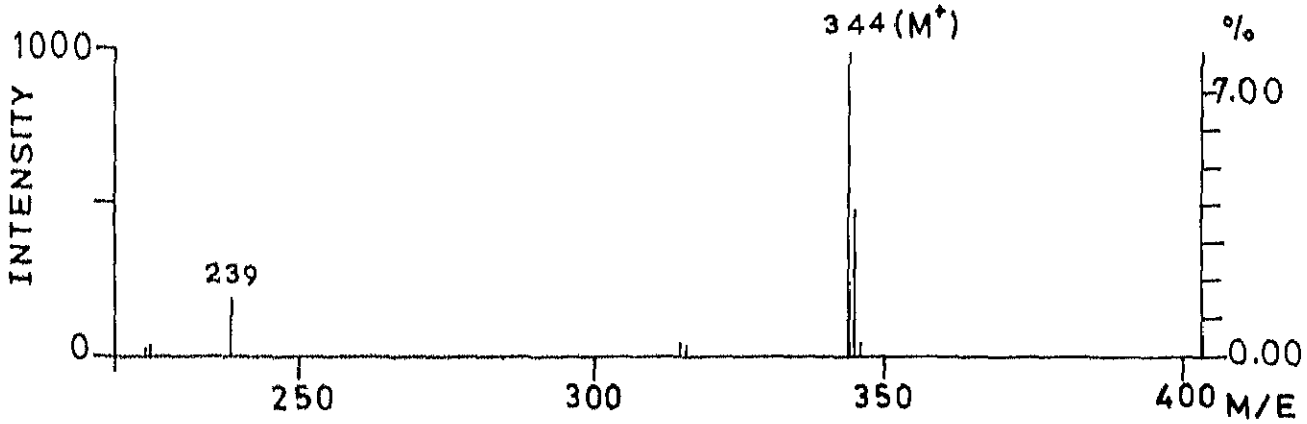


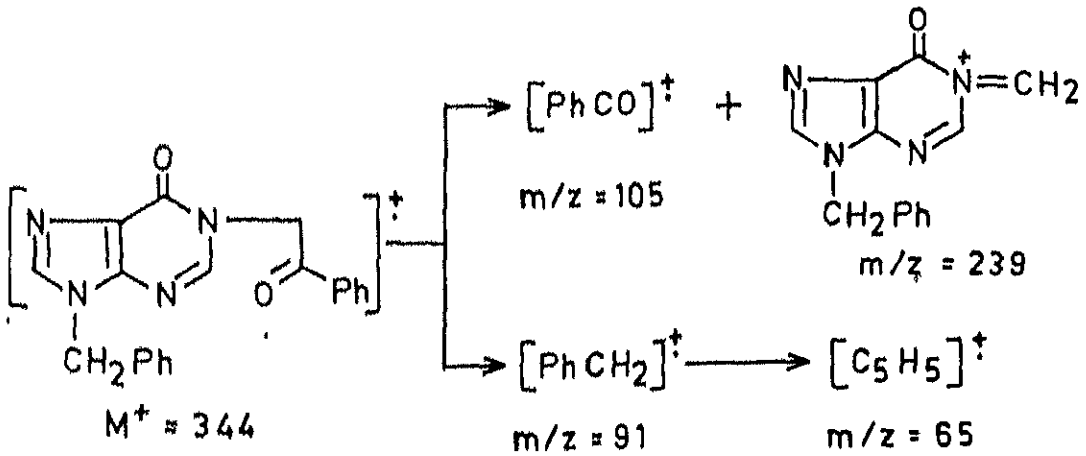


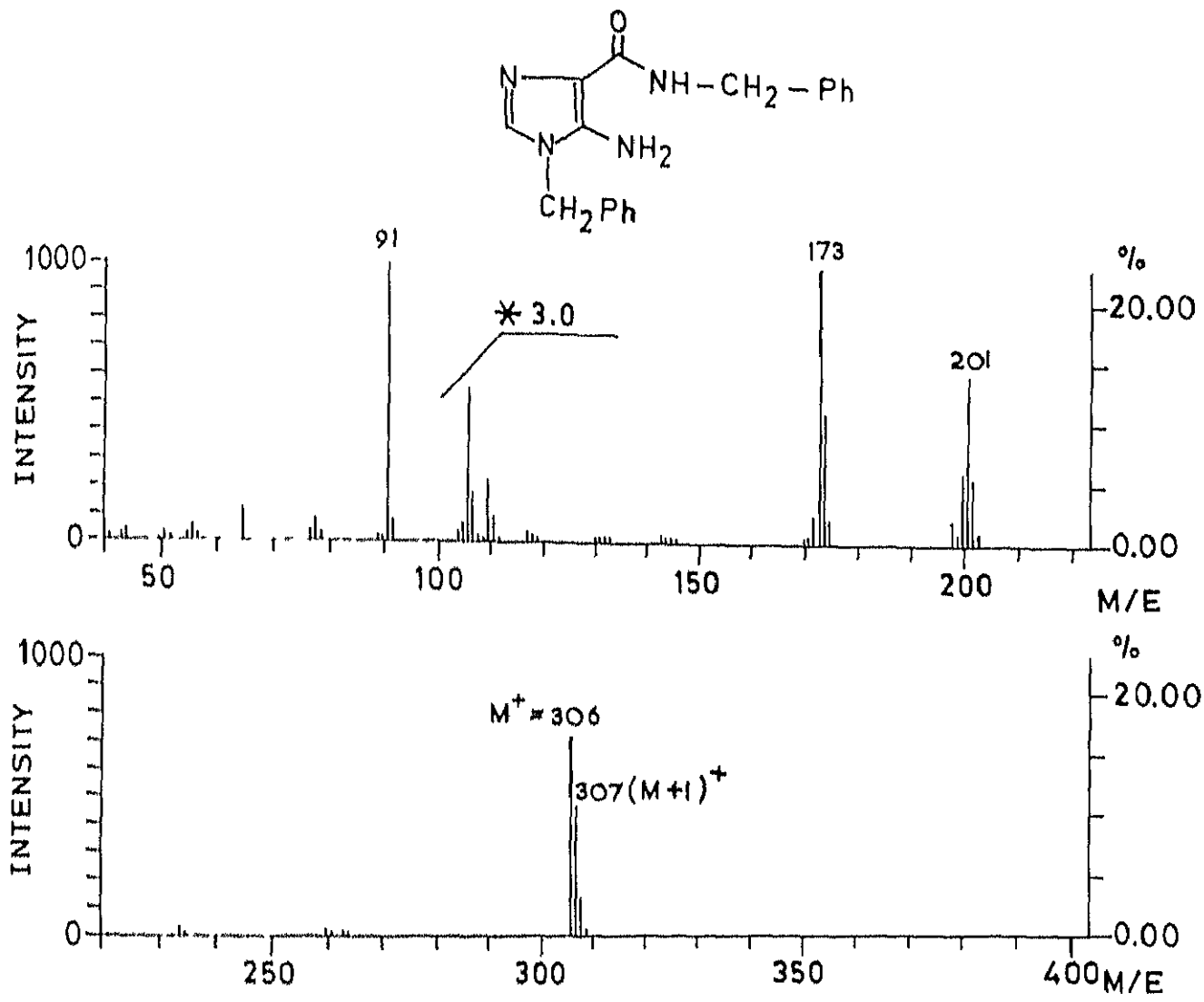


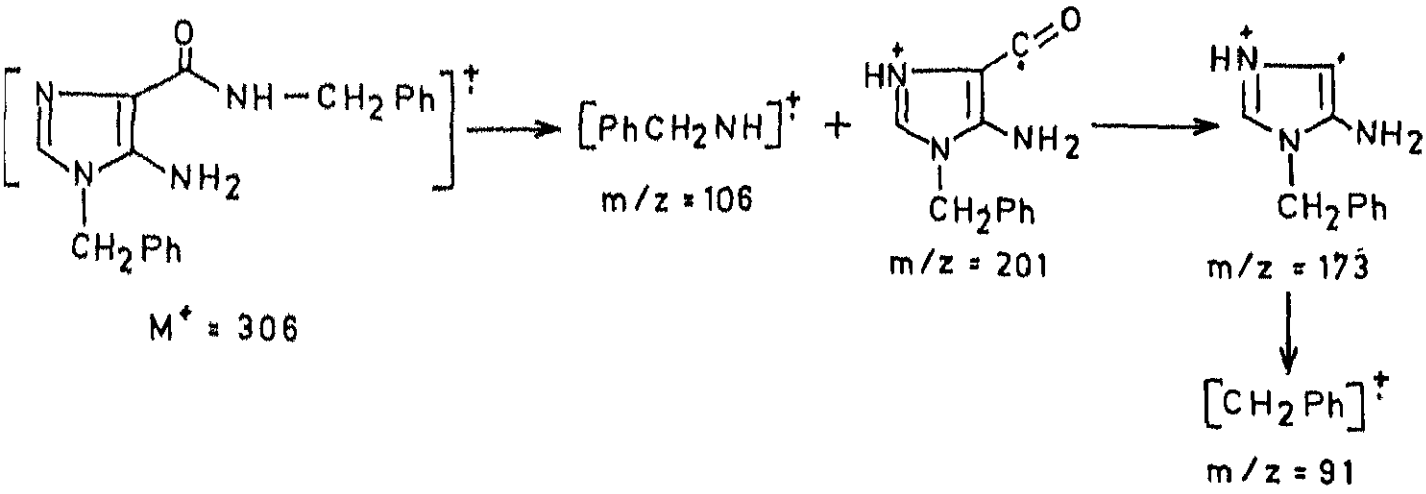
$M^{+\cdot} = 226$ $m/z = 144$

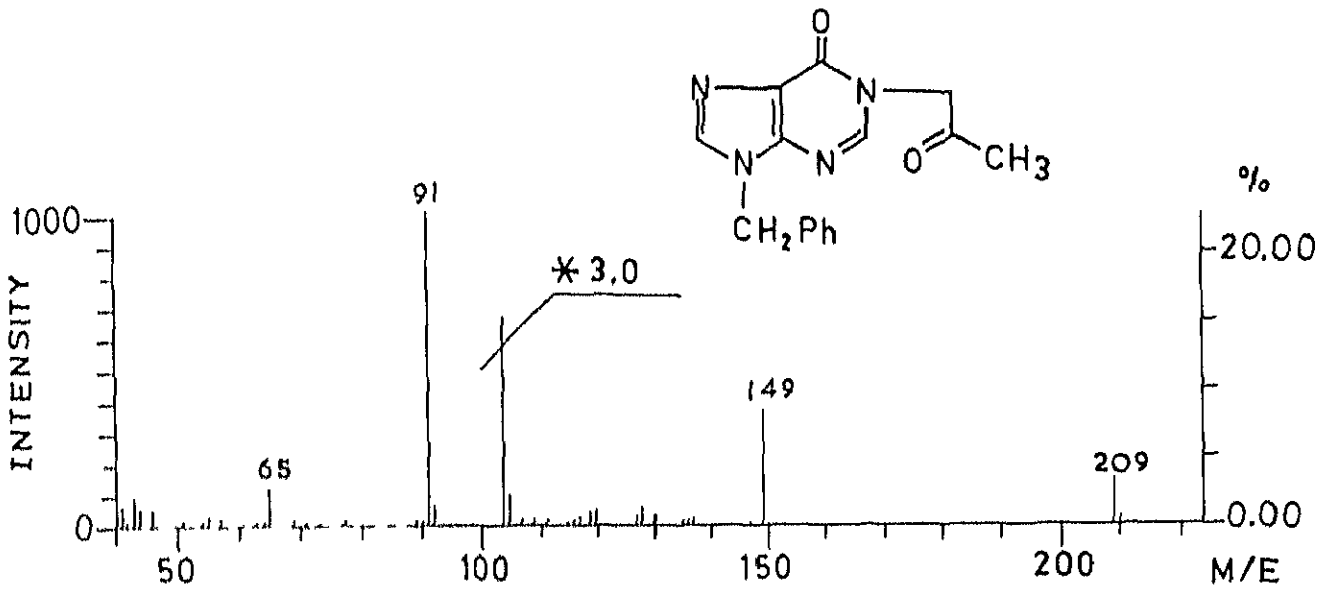

1000
INTENSITY
0
91
105
65
50
100
150
200
%
7.00
0.00
M/E

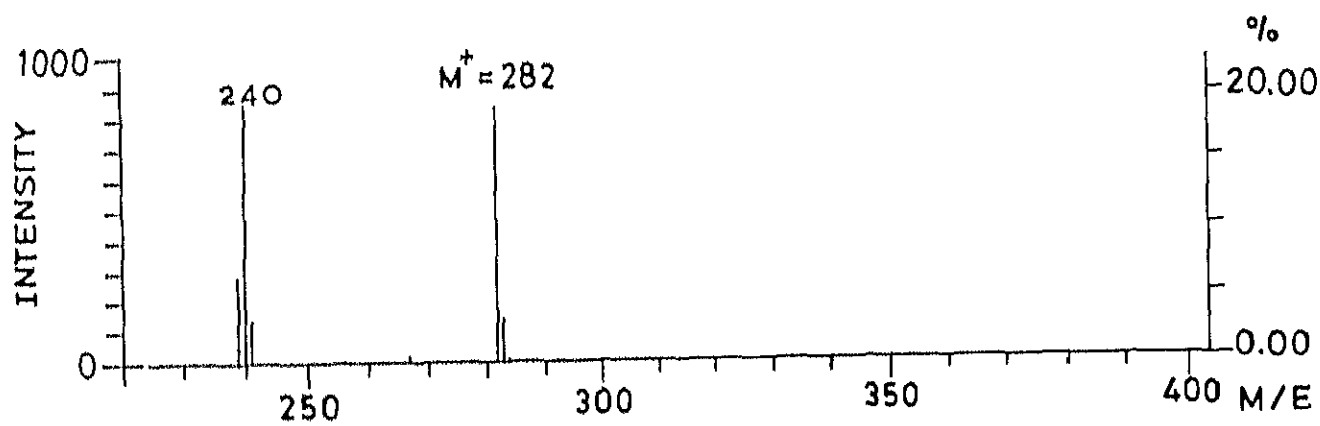

1000
INTENSITY
0
344 (M+)
239
250
300
350
400
%
7.00
0.00
M/E

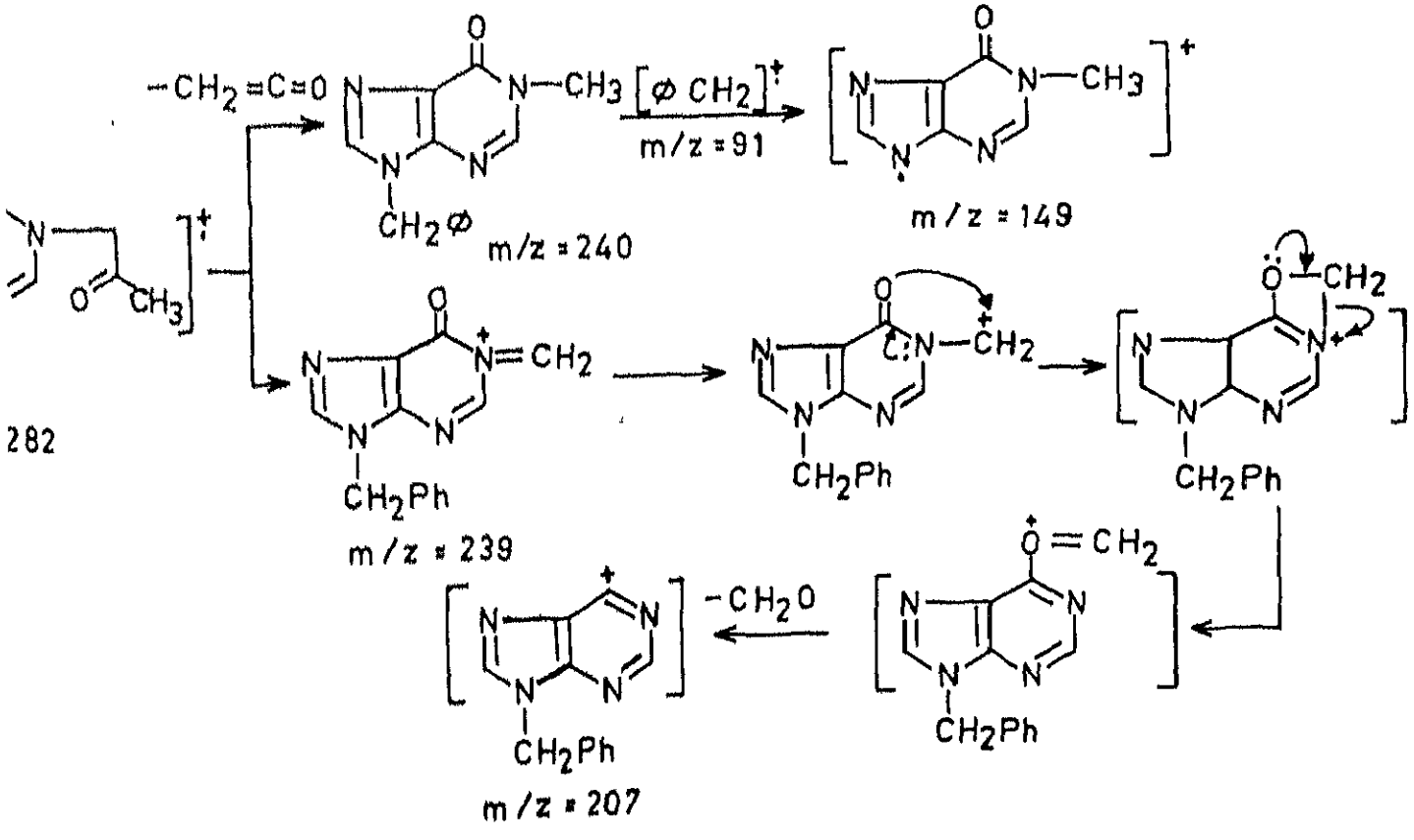

[PhCO]+
m/z = 105
+
CH2=
CH2Ph
m/z = 239
[PhCH2]+
[C5H5]+
m/z = 91
m/z = 65
M+ = 344

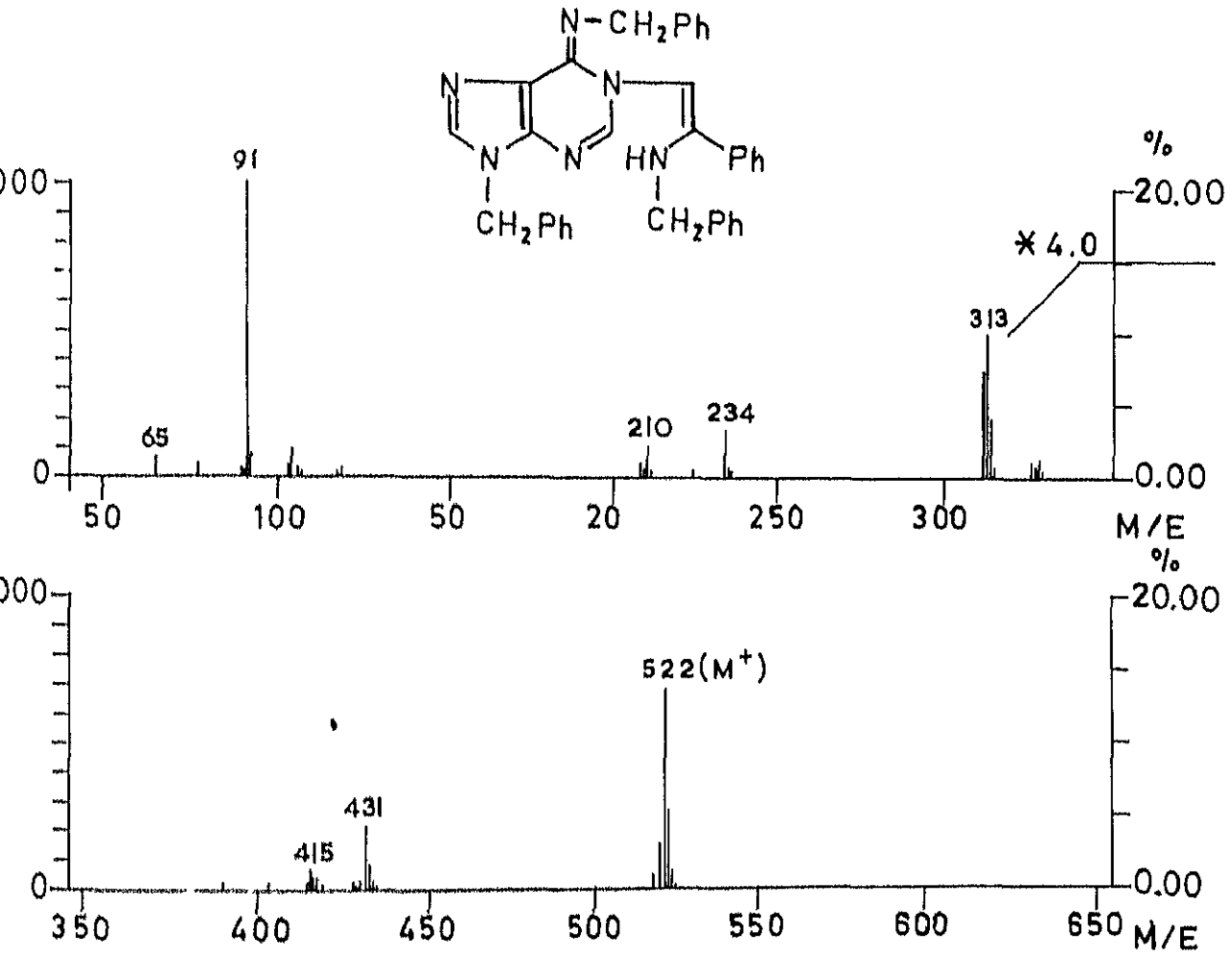

INTENSITY
1000
0
91
* 3.0
173
201
%
20.00
0.00
50
100
150
200
M/E
INTENSITY
1000
0
M+ = 306
307(M+1)+
%
20.00
0.00
250
300
350
400
M/E

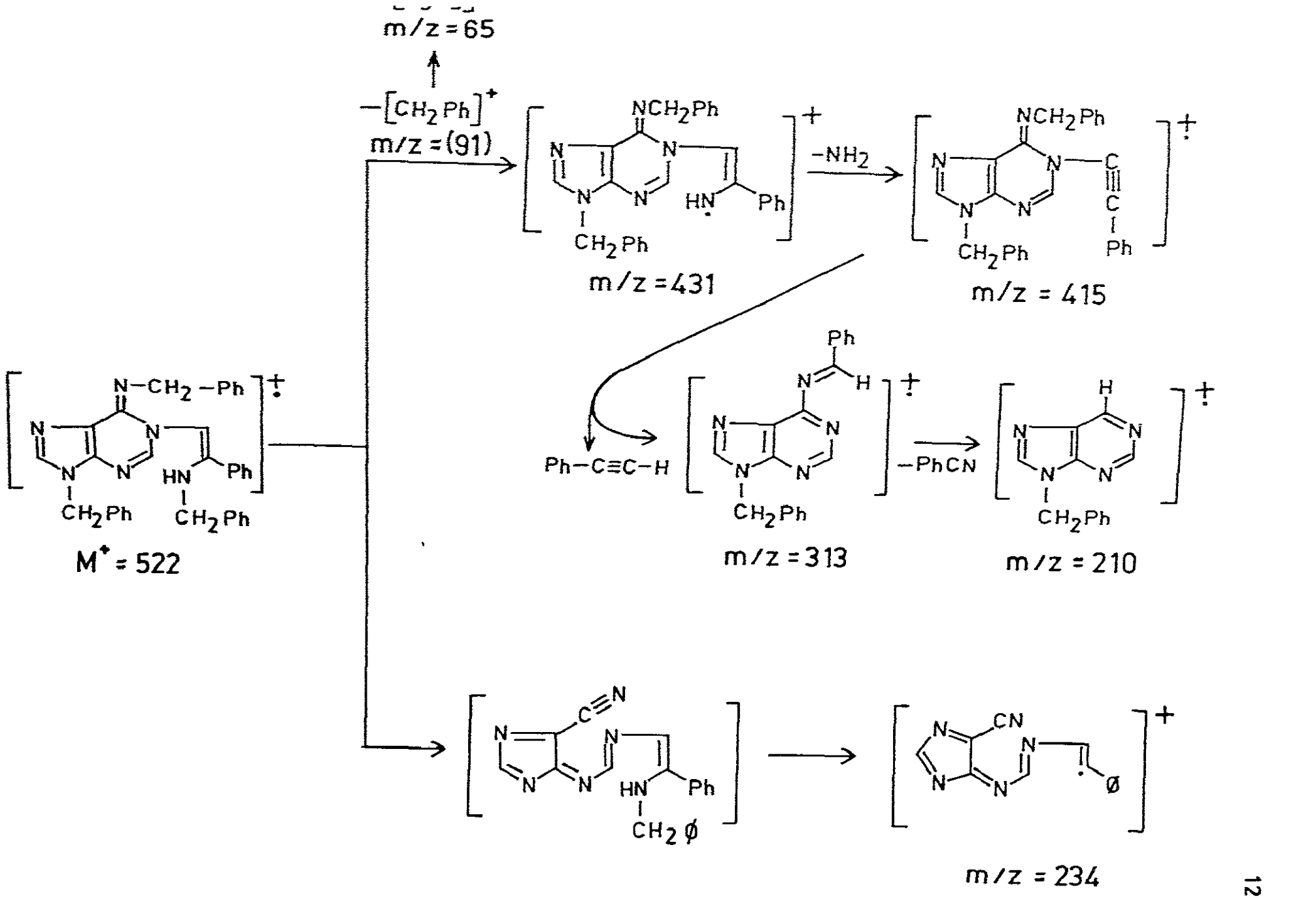

NH – CH2 Ph
NH2
CH2 Ph
M+ = 306
[PhCH2NH]+
m/z = 106
m/z = 201
m/z = 173
[CH2 Ph]+
m/z = 91

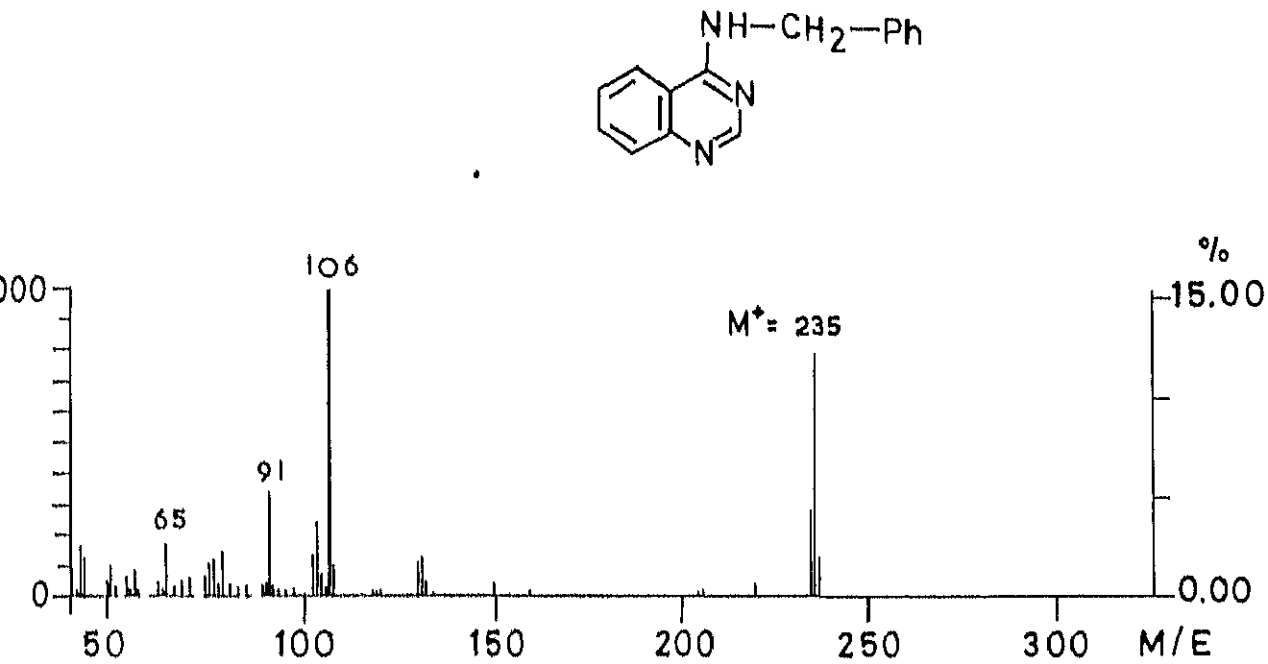

1000
INTENSITY
0
91
* 3,0
65
149
209
50
100
150
200
M/E
%
20.00
0.00

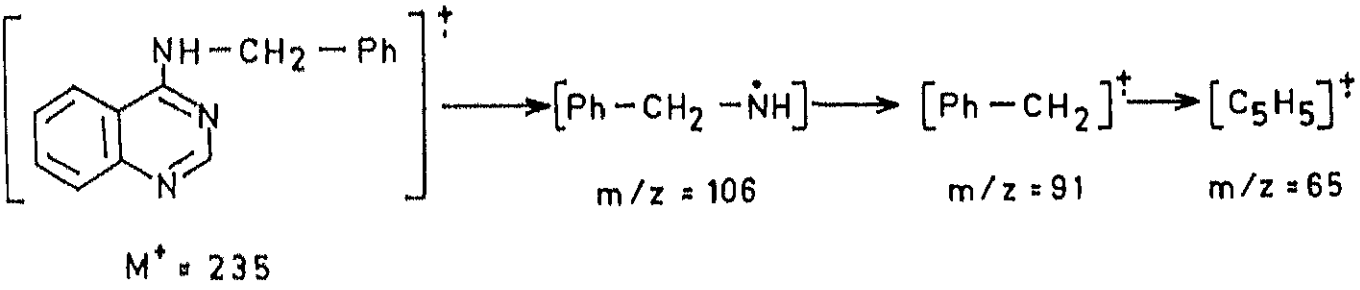

1000
INTENSITY
0
240
M+ = 282
250
300
350
400
M/E
%
20.00
0.00


-CH2=C=O
[ø CH2]+
m/z = 91
m/z = 149
m/z = 240
m/z = 239
282
-CH2O
m/z = 207

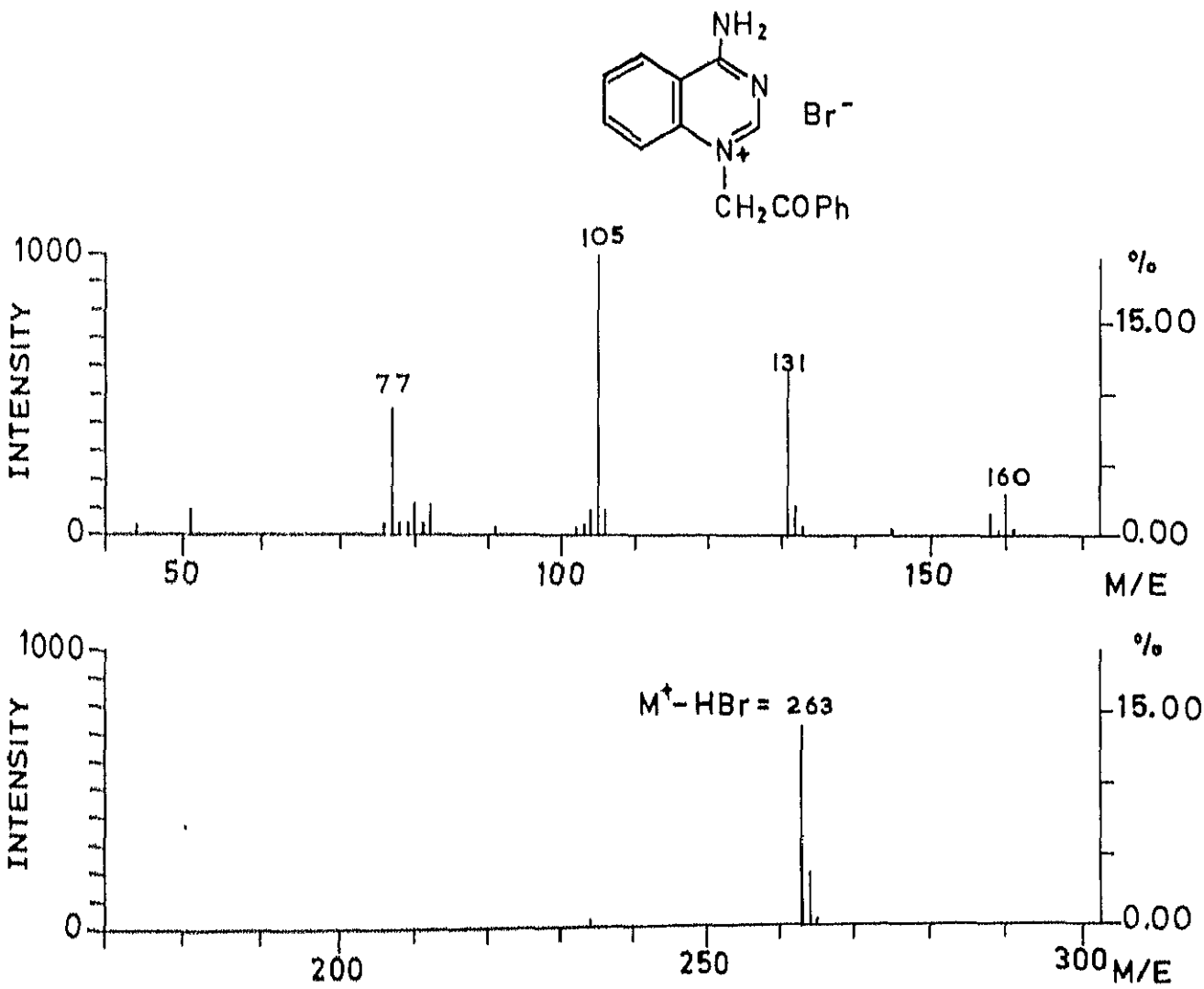

N-CH2Ph
N
N
N
N
HN
Ph
CH2Ph
CH2Ph
91
65
210
234
313
%
20.00
*4.0
0.00
M/E
50
100
50
20
250
300
522(M+)
431
415
350
400
450
500
550
600
650

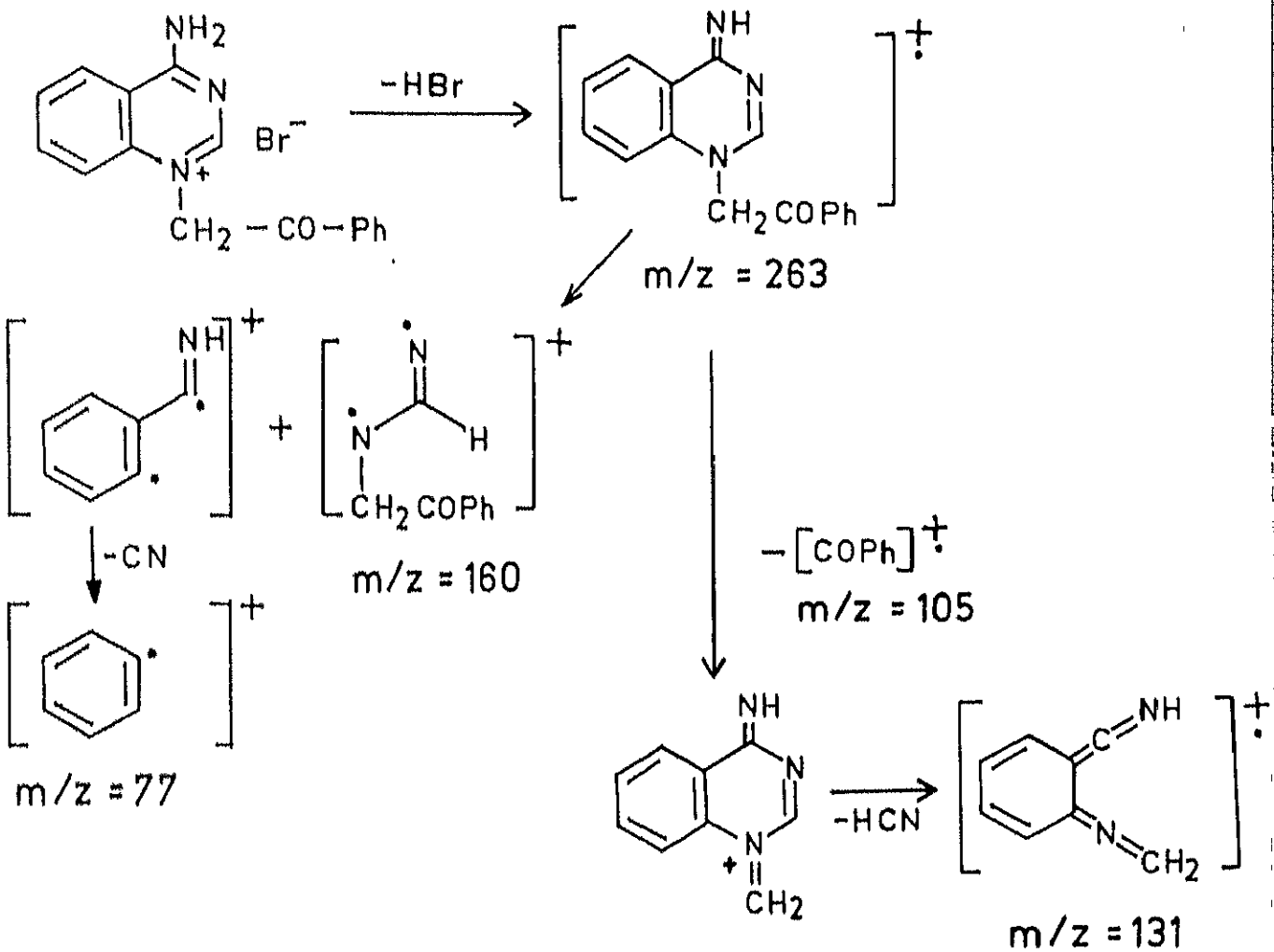

m/z = 65
−[CH2Ph]+
m/z = (91)
−NH2
m/z = 431
m/z = 415
Ph−C≡C−H
−PhCN
m/z = 313
m/z = 210
M+ = 522
m/z = 234


NH–CH2–Ph
N
N
%
15.00
0.00
106
M+= 235
91
65
0
50
100
150
200
250
300
M/E


NH–CH2–Ph
N
N
[Ph–CH2–NH]
[Ph–CH2]+
[C5H5]+
m/z = 106
m/z = 91
m/z = 65

$M^+ = 235$


NH2
N
Br⁻
N+
CH2COPh
1000
INTENSITY
0
105
77
131
160
%
15.00
0.00
50
100
150
M/E
1000
INTENSITY
0
M+-HBr = 263
%
15.00
0.00
200
250
300
M/E


NH2
N
N+
Br−
CH2 − CO − Ph
-HBr
NH
N
N
CH2COPh
m/z = 263
NH
N
N
H
CH2COPh
m/z = 160
-CN
m/z = 77
−[COPh]+·
m/z = 105
NH
N
N+
CH2
-HCN
NH
C
N
CH2
m/z = 131

1.E. EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 580 spectrophotometer either as neat liquids or as thin KBr discs. NMR spectra were obtained on 10-15% solutions in $CDCl_3$ or CCl_4 or DMSO-d_6 on a FT-R-600 instrument. The chemical shifts are recorded in ppm with TMS at 0.00 as internal standard. Mass spectra were obtained on a Jeol instrument. Elemental analysis were carried out in automatic C, H, N analysers. Silica Gel G (ACME) was used for tlc and also for column chromatography (100-200 mesh). Reactions were monitored wherever possible by TLC. The organic extracts were invariably dried over anhydrous $MgSO_4$ and solvents evaporated *in vacuo*.

I. The reaction of anthranilic acid with formamide:

Preparation of 4-quinazolone (4):

Anthranilic acid (45) (54.8 g, 400 mmol) was admixed with formamide (30.4 g, 675 mmol), held first at 135°C for 3 hours and then at 170-180°C for 2 hours, during which the evolution of ammonia ceased and the product solidified to a cake. This was pulverized, extracted with hot water (700 ml), filtered and crystallized from boiling water (750 ml) to give 50 g (85%) of 4-quinazolone (4), mp 216°C (lit.[5] mp 216°C).

ir : ν_{max} (KBr) cm^{-1} : 3200, 3170 (amide NH), 1700 (amide carbonyl).

II. The reaction of anthranilamide (2) with DMF-acetal. Preparation of 4-quinazolone (4):

A mixture of anthranilamide (2) (0.680 g, 5 mmol), dimethyl acetal of dimethyl formamide (1 ml) and dry benzene (10 ml) was held at reflux for 12 hours, cooled, filtered and washed with benzene to yield 0.400 g (55%) of 4-quinazolone, mp 215°C (lit.[4] mp 216°C).

ir : ν_{max} (KBr) cm^{-1} : 3200, 3170 (-NH), 1700 (amide carbonyl).

III. The reaction of 4-quinazolone (4) with o-phenylenediamine: Isolation of 3-(o-aminophenyl) 4-quinazolone (5):

A mixture of 4 (4.38 g, 30 mmol) - prepared from anthranilamide (2) and DMF-acetal[4] - and o-phenylenediamine (3.24 g, 30 mmol) was held at 190-200°C for 3 hours; chromatography of the residue on silica gel and elution with PhH:EtOAc::30:70 gave 0.71 g (10%) of 5. Yellowish brown needles, mp 140°C.

tlc : PhH:EtOAc::50:50; Rf.0.5

Anal. Cald. for $C_{14}H_{11}N_3O$ (Mol. Wt. 237)

C, 70.88;H,4.64; N, 17.72%

Found: C, 70.59; H, 4.85; N, 17.99%

ir : ν_{max} (KBr) cm^{-1}; 3300-2800 (NH_2), 1690 (C=O), 1615, 1565 (C=C, C=N)

m/z : 146, 119, 91.

IV. The reaction of 5 with aqueous NaOH: Isolation of derived product benzimidazole and anthranilic acid:

A suspension of 5 (0.1 g, 0.42 mmol) in aqueous NaOH (1N, 10 ml) was refluxed for 12 hours, cooled, extracted with $CHCl_3$ (3x20 ml), dried, evaporated and the residue on crystallization from benzene gave benzimidazole, mp 170°C (lit. mp 170-173°C), yield 0.037 g (73%).

The aqueous layer was adjusted to pH ~ 7 with $2NH_2SO_4$,

extracted with $CHCl_3$ (3x20 ml), dried, evaporated and the residue on crystallization from benzene gave 0.046 g (79%) of anthranilic acid, mp 146°C (lit. mp 144-146°C).

V. The reaction of 4-quinazolone (4) with phenacyl bromide: Preparation of 3-phenacyl-4-quinazolone (6):

Phenacyl bromide (7.96 g, 40 mmol) was added to a solution of the potassium salt of 4 in MeOH-prepared from 0.58 M KOH in dry MeOH (100 ml) and 4 (5.84 g, 40 mmol) - and the solution left stirred at rt. overnight, filtered, the filtrate evaporated and the residue chromatographed on a short column of silica gel. Elution with PhH:EtOAc::70:30 gave 6 as colourless prisms, mp 159°C, yield 4.2 g (40%).

tlc : PhH:EtOAc::80:20; Rf. 0,5

Anal. Cald. for $C_{16}H_{12}N_2O_2$ (Mol. Wt. 264)
C, 72.72; H, 4.54; N, 10.60%)

Found: C, 72.80; H, 4.39; N, 10.82%

ir : ν_{max}(KBr) cm^{-1} : 1690 (C=0),
1665 (amide carbonyl)

nmr : $\delta(CDCl_3)$,60 MHz : 5.45 (s, 2H, $-C\underline{H}_2$),
7.35-8.45 (m, 10H, aromatic)

m/z : 264 (M^+), 159 (M^+ - PhCO).

VI. The reaction of 4-quinazolone (4) with bromoacetone: Preparation of 3-acetonyl 4-quinazolone (7)

The reaction of bromoacetone (6 g, 43 mmol) with the potassium salt of 4 in MeOH-prepared from 0.53 M KOH (100 ml) and 4 (5.84 g, 40 mmol) - as described in Experiment V, gave 4 g (50%) of 7 : colourless needles, mp 158°C (lit.[27] mp 159°C).

tlc : PhH:EtOAc::80:20; Rf. 0.3

Anal. Cald. for $C_{11}H_{10}N_2O_2$ (Mol. Wt. 202)

C, 65.35; 4.95; N, 13.86%

Found: C, 65.80, H, 5.25, N, 13.77%

ir : ν_{max}(KBr) cm^{-1}, 1720 (C=O), 1675, 1610 (amide carbonyl, C=C)

nmr : $\delta(CDCl_3)$, 60 MHz : 2.35 (s, 3H, $-COCH_3$), 4.85 (s, 2H, $-CH_2$), 7.3-8.4 (m, 5H , aromatic)

m/z : 202 (M^+), 159 ($M^+ - COCH_3$)

VII. The reaction of 3-phenacyl, 4-quinazolone (6) with benzyl amine: Isolation of the derived imidazole 8 and modified parent 10:

A stirred mixture of 6 (0.528 g, 2 mmol) benzylamine (0.856 g, 8 mmol), anhyd. p-TsOH (0.76 g, 4 mmol) and dry xylene (50 ml) was refluxed for 12 hours, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::80:20 gave 0.31 g (71%) of anthranil-benzylamide (10), mp 123°C (lit.[28] mp 123°C).

tlc : PhH:EtOAc::80:20; Rf. 0.7

ir : ν_{max} (KBr) cm^{-1}; 3480, 3310 (NH_2, NH), 1630 (amide carbonyl)

nmr : δ ($CDCl_3$), 60 MHz : 4.55 (d, 2H, $-C\underline{H}_2Ph$), 5.25 (br, 2H, $-N\underline{H}_2$), 6.7-7.5 (m, 10H, aromatic).

Further elution with PhH:EtOAc::60:40 gave 0.33 g (69%) of the template product, 1-benzyl-5-phenyl imidazole (8) as colourless needles from benzene, mp 111°C.

tlc : PhH:EtOAc::80:20; Rf. 0.3

Anal. Cald. for $C_{16}H_{14}N_2$ (Mol. Wt. 234)

C, 82.05; H, 5.98; N, 11.97%

Found: C, 81.76; H, 5.44; N, 11.80%

nmr : δ ($CDCl_3$), 60 MHz: 5.1 (s, 2H, $-C\underline{H}_2Ph$), 6.7-7.9 (m, 12H, aromatic)

m/z : 234 (M^+).

VIII. The reaction of 3-acetonyl 4-quinazolone (7) with benzylamine: Isolation of the daughter imidazole 9 and the modified parent 10:

The reaction of 7 (0.606 g, 3 mmol) with benzylamine (1.28 g, 12 mmol) and p-TsOH (1.14 g, 6.6 mmol) in dry xylene, (50 ml) when carried out exactly as described in Experiment VII,

gave 0.3 g (45%) of anthranilbenzylamide (10) and 0.284 g (55%) of the derived product, 1-benzyl 5-methyl imidazole (9) mp 99°C.

tlc : PhH:EtOAc::80:20, Rf. 0.3

Anal. Calcd. for $C_{11}H_{12}N_2$ (Mol. Wt. 172)

C, 76.74; H, 6.97; N, 16.28%

Found: C, 76.40; H, 6.30; N, 16.57%

nmr : $\delta(CDCl_3)$, 60 MHz: 2.1 (s, 3H, $-CH_3$), 5.05 (s, 2H, $-CH_2Ph$), 6.85-8.2 (m, 7H, aromatic)

m/z : 172 (M^+).

IX. The reaction of anthranilbenzylamide (10) with methane sulphonic acid: Regeneration of the parent 2:

A stirred mixture of 10 (0.363 g, 1.6 mmol), MsOH (1.54 g, 16 mmol) and dry xylene (15 ml) was refluxed for 10 hours, solvents evaporated, neutralized with aqueous ammonia, extracted with $CHCl_3$ (3x20 ml), dried and evaporated. The residue on chromatography over a short column of silica gel and elution with PhH:EtOAc::1:1 gave 0.185 g (84%) of anthranilamide (2) mp 110°C (lit. mp 110°C).

tlc : PhH:EtOAc::90:10; Rf. 0.8

ir : ν_{max}(KBr) cm^{-1}; 3440, 3060 (br, NH_2), 1710 (amide carbonyl).

X. The reaction of 3-phenacyl 4-quinazolone (6) with octadecylamine: Isolation of daughter product 1-octadecyl 5-phenyl imidazole (11) and anthraniloctadecylamide (13):

A stirred mixture of 6 (0.528 g, 2 mmol), octadecylamine (2.15 g, 8 mmol), anhyd. p-TsOH (0.95 g, 5 mmol) and dry xylene (40 ml) was refluxed for 18 hours, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::80:20 gave 0.27 g (35%) of 13; colourless crystals, mp. 86-87°C.

tlc : PhH:EtOAc::50:50; Rf. 0.7

ir : ν_{max}(KBr) cm^{-1}; 3500, 3400, 3330, (NH_2, NH), 1640 (C=O), 1590, 1550 (C=C, C=N)

nmr : $\delta(CDCl_3)$, 60 MHz: 0.63-1.73 (m+s, 35H, $-CH_2-(CH_2)_{16}-CH_3$), 3.33 (m, 2H, $-CH_2-(CH_2)_{16}-CH_3$), 5.2 (s, 2H, NH_2), 6.05 (br, 1H, -CONH), 6.43-7.43 (m, 4H, aromatic).

m/z : 388 (M^+).

Further elution with PhH:EtOAc::70:30 afforded template product 11 (0.26 g, 33%) as a low melting solid.

tlc : PhH:EtOAc::50:50; Rf. 0.3

nmr : $\delta(CDCl_3)$, 60 MHz: 0.6-1.75 (m+s, 35H, $-CH_2-(CH_2)_{16}-CH_3$), 3.95 (t, 2H, $-CH_2-(CH_2)_{16}-CH_3$), 6.95-7.85 (m+s, 7H, aromatic)

m/z : 396 (M^+).

XI. The reaction of 3-acetonyl 4-quinazolone (7) with octadecylamine: Isolation of the derived product, 1-octadecyl 5-methyl imidazole (12) and amide 13:

The reaction of 3-acetonyl 4-quinazolone (7) (1 g, 5 mmol) and octadecylamine (4 g, 15 mmol), promoted by p TsOH (1.9 g, 10 mmol) in dry xylene (40 ml), when carried out precisely as described in Experiment X gave 0.612 g (31%) of anthranilloctadecylamide (13) mp 86-87°C and 0.296 g (18%) of the derived imidazole 12 as a low melting solid.

tlc : PhH:EtOAc::70:30; Rf. 0.17

nmr : δ($CDCl_3$), 60 MHz: 0.65-1.85 (m, 35H, $-CH_2-(CH_2)_{16}-CH_3$), 2.27 (s, 3H, $-CH_3$), 3 80 (t, 2H, $-CH_2-(CH_2)_{16}-CH_3$) 7.25 (s, 1H, aromatic), 7.35 (s, 1H, aromatic).

m/z : 334 (M^+).

XII. The reaction of 3-phenacyl 4-quinazolone (6) with cyclohexyl amine: Isolation of the daughter product 1-cyclohexyl 5-phenyl imidazole (14) and anthranilcyclohexylamide (15):

The reaction of 6 (0.528 g, 2 mmol) and cyclohexylamine (0.792 g, 8 mmol), promoted by anhyd. p-TsOH (0.76 g, 4.4 mmol) in dry xylene (50 ml), when carried out precisely as described

in Experiment VII gave 0.115 g (65%) of anthranilcyclohexylamide (15), mp 154°C (lit.[28] mp 154°C).

tlc : PhH:EtOAc::80:20; Rf. 0.7

ir : ν_{max}(KBr) cm^{-1}; 3470, 3360, 3290 (NH), 1620 (amide carbonyl)

nmr : $\delta(CDCl_3)$, 60 MHz: 0.6-2.3 (m, 10H, $-C_6\underline{H}_{11}$), 3.85 (br, 1H, $C_6\underline{H}_{11}$), 5.5 (br, 2H, $-N\underline{H}_2$), 5.9 (br, 1H, -CON<u>H</u>), 6.4-7.3 (m, 4H, aromatic).

Further elution with PhH:EtOAc::60:40 gave 0.14 g (70%) of the derived product 1-cyclohexyl 5-phenyl imidazole, colourless thick liquid bp. 180°C/0.1 torr.

tlc : PhH:EtOAc::80:20; Rf. 0.3

Anal. Calc. for $C_{15}H_{18}N_2$ (Mol. Wt. 226)

C, 79.65; H, 7.96; N, 12.38%

Found: C, 79.35; H, 7.48; N, 12.40%

nmr : $\delta(CDCl_3)$, 60 MHz: 1-2.35 (m, 10H, $-C_6\underline{H}_{11}$), 3.85 (br, 1H, $-C_6\underline{H}_{11}$), 7.35 (br, s, 7H, aromatic)

m/z : 226 (M^+).

XIII. <u>The reaction of 1-benzyl 5-aminoimidazole 4-carboxamide (1) with formamide: The preparation of 9-benzyl hypoxanthine (3):</u>

A mixture of 1 (0.170 g, 0.8 mmol) and formamide (0.7 ml, excess) was held at 195°C for 0.75 hours, cooled,

admixed with ice-cold water (5 ml), filtered and crystallized from hot water to give 0.120 g (67%) of 3, mp 291°C (lit.[29] 297°C).

ir : ν_{max} (KBr) cm^{-1}; 1700 (amide carbonyl), 1590 1550, 1520 (C=C, C=N)

XIV. The reaction of 9-benzyl hypoxanthine with phenacyl bromide: Preparation of 1-phenacyl 9-benzyl hypoxanthine (16):

Phenacyl bromide (1.86 g, 9 mmol) was added to a solution of the potassium salt of 9-benzyl hypoxanthine in MeOH-prepared from 0.41 M KOH in dry MeOH (50 ml) and 9-benzyl hypoxanthine (1.06 g, 4.6 mmol) - the reaction mixture left stirred at rt., overnight, filtered, the filtrate evaporated and the residue chromatographed on silica gel. Elution with $CHCl_3$:MeOH:96:4 gave 1.3 g (82%) of 16 as colourless prisms, mp 201°C.

tlc : $CHCl_3$:MeOH::90:10; Rf. 0.7

Anal. Cald. for $C_{20}H_{16}N_4O_2$ (Mol. Wt. 344)
C, 69.76; H, 4.65; N, 16.28%

Found: C, 69.32; H, 4.15; N, 16.61%

ir : ν_{max} (KBr) cm^{-1}, 1700 (carbonyl), 1610, 1590 (C=C, C=N)

nmr : δ(CDCl$_3$), 60 MHz: 5.3 (s, 2H, $-C\underline{H}_2COPh$), 5.5(s,2H, $-C\underline{H}_2Ph$), 7.2-8.2 (m, 12H, aromatic)

m/z : 344 (M^+), 239 (M^+ - PhCO).

XV. The reaction of 1-phenacyl 9-benzyl hypoxanthine (16) with benzylamine: Isolation of the derived imidazole (8) and the modified parent imidazole (17):

A stirred mixture of 16 (0.344 g, 1 mmol), benzylamine (0.428 g, 4 mmol), anhyd. p-TsOH (0.57 g, 3 mmol) and dry xylene (30 ml) was refluxed for 12 hours, cooled, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::1:1 gave 0.084 g (36%) of the daughter product 1-benzyl 5-phenyl imidazole (8) mp 111°C.

Further elution with PhH:EtOAc::2:3 afforded 0.1 g (33%) of 5-amino-1, N-dibenzyl imidazole 4-carboxamide; colourless prisms, mp 159-160°C (lit.[30] mp 161°C).

tlc : $CHCl_3$:MeOH::80:20 , Rf. 0.3

ir : ν_{max}(KBr) cm^{-1}, 3400, 3300 (-NH), 1630 (amide carbonyl)

nmr : $\delta(CDCl_3)$, 60 MHz: 4.45 (d, 2H, $-CONHC\underline{H}_2Ph$, + D_2O s), 4.7 (br, 2H, $-N\underline{H}_2$, exch. D_2O), 4.8 (s, 2H, $-C\underline{H}_2Ph$), 6.8-7.7 (m, 12H, $-N\underline{H}$ and aromatic).

m/z : 306 (M^+).

XVI. The reaction of 9-benzyl hypoxanthine (3) with bromoacetone: Preparation of 1-acetonyl 9-benzyl hypoxanthine (18):

The reaction of bromoacetone (1.3 g, 9 mmol) with the potassium salt of 9-benzyl hypoxanthine in MeOH-prepared from 0.14 M KOH in dry MeOH (50 ml) and 9-benzyl hypoxanthine (1.06 g, 4.6 mmol) - done precisely as described in Experiment XIV, gave 0.83 g (66%) of 18, colourless needles, mp 155-158°C.

tlc : $CHCl_3$:MeOH::90:10; Rf. 0.5

Anal. Cald. for $C_{15}H_{14}N_4O_2$ (Mol. Wt. 282)

C, 63.83; H, 4.96; N, 19.86%

Found: C, 64.10; H, 5.30; N, 19.35%

ir : ν_{max}(KBr) cm^{-1}; 1715 (br, C=O)

nmr : $\delta(CDCl_3)$, 60 MHz : 2.25 (s, 3H, $-COC\underline{H}_3$), 4.95 (s, 2H, $-C\underline{H}_2COCH_3$), 5.3 (s, 2H, $-C\underline{H}_2Ph$), 7.3 (s, 5H, phenyl), 7.75 (s, 1H, imidazolyl proton), 7.95 (s, 1H, pyrimidyl proton)

m/z : 282 (M^+), 239 ($M^+ - \cdot COCH_3$).

XVII. The reaction of 1-acetonyl 9-benzyl hypoxanthine (18) with benzylamine: Isolation of the derived imidazole 9 and the modified parent imidazole 17:

A stirred mixture of 18 (0.282 g, 1 mmol), benzylamine (0.428 g, 4 mmol), anhyd. p-TsOH (0.57 g, 3 mmol) and dry xylene (30 ml) was refluxed for 12 hours, solvents evaporated and the residue chromatographed on silica gel. Elution with PhH:EtOAc::1:1 gave 0.050 g (30%) of the derived product 1-benzyl 5-methyl imidazole (9) mp 99°C. Further elution with PhH:EtOAc::2:3 gave 0.079 g (26%) of 5-amino-1, N-dibenzyl imidazole 4-carboxamide (17) as colourless prisms, mp 161°C.

XVIII. The reaction of 5-amino, 1, N-dibenzyl imidazole-4-carboxamide (17) with methanesulphonic acid: Regeneration of parent 1:

A stirred mixture of 17 (0.28 g, 0.9 mmol) and MsOH (1.5 ml, excess) was held at 125-130°C for 3 hours, cooled, added to cold water (~ 10 ml), neutralised with aqueous ammonia, filtered, washed with cold water and dried. Crystallization from ethanol gave 0.176 g (88%) of 1, colourless prisms, mp 256°C (lit.[29] mp 257°C).

XIX. The transformation of the daughter product 5-methyl 1-benzyl imidazole (9) to dl-histidine:

5-Formyl 1-benzyl imidazole (30):

A mixture of 9 (0.172 g, 1 mmol), SeO_2 (0.120 g, 1.2 mmol) and glacial AcOH (5 ml) was refluxed for 10 hours, evaporated and the residue chromatographed on silica gel. Elution with EtOAc::MeOH:80:20 gave 0.066 g (35%) of 5-formyl 1-benzyl imidazole which was used as such in the following experiment.

ir : ν_{max} (neat) cm^{-1}; 1690 (-CHO)

5-Hydroxy methyl 1-benzyl imidazole (28):

A solution of the above aldehyde in dry MeOH (10 ml) was admixed with $NaBH_4$ (0.100 g, 2.38 mmol), left stirred at rt. for 5 hours, evaporated and chromatographed on silica gel. Elution with EtOAc::MeOH:80:20 gave 0.041 g (61%) of 5-hydroxy methyl 1-benzyl imidazole mp 134°C (lit.[16] mp, 134-135°C) identical to an authentic sample prepared from D-fructose.

tlc : PhH:EtOAc::50:50; Rf. 0.4

nmr : δ ($CDCl_3$), 60 MHz: 4.46 (s, 2H, $-C\underline{H}_2OH$)
4.7 (s, 1H, $-CH_2O\underline{H}$), 5.14 (s, 2H, $-C\underline{H}_2Ph$),
6.61-7.91 (m, 7H, aromatic)

4(5)-Hydroxy methyl imidazole (31):

The deprotection was achieved in quantitative yields by hydrogenation over Pd/c Picrate, mp 202-203°C (lit.[13] mp 203°C).

dl-Histidine (34):

4(5)-Hydroxy methyl imidazole was transformed to dl-histidine by known procedures[14,15]. The amino acid thus obtained was identical in all respects to an authentic sample.

XX. 9-Benzyl adenine (19):

Sodium salt of adenine:

A suspension of adenine (5 g, 37 mmol) and NaH (0.65 g, 27 mmol as 50% dispersion in mineral oil) in dry DMF (60 ml) was left stirred at rt. for 3 hours. The resulting white suspension of the sodium salt was used as such in the next experiment.

9-Benzyl adenine (19):

To the stirred suspension of sodium salt of adenine was added in drops benzylbromide (5 ml, 42 mmol) and the resulting mixture left stirred at rt. for 24 hours, refrigerated overnight, filtered and crystallized from 95% ethanol to give 2.25 g (27%) of 19 mp 232-233°C (lit.[18] mp. 234-236°C).

nmr : δ(DMSO-d_6), 100 MHz: 5.4 (s, 2H, -C$\underline{H}_2$Ph), 7.3 (m, 5H, phenyl), 8.0 (s, s, 1H, 1H).

XXI. The reaction of 9-benzyl adenine (19) with phenacyl bromide: Preparation of the bis-alkylated salt 20:

A stirred solution of 19 (2.25 g, 10 mmol) and phenacyl bromide (3 g, 15 mmol) in dry DMF (50 ml) was left stirred, overnight at rt., evaporated, the residue washed with dry ether (3 times) and crystallized from absolute MeOH to give 2.218 g (35%) of 20; colourless prisms, mp 219-223°C

Anal. Cald. for $C_{28}H_{25}N_5O_2Br_2$ (Mol. Wt. 623)
C, 53.9; H, 4.0; N, 11.2%

Found: C, 55.68; H, 4.43; N, 10.82%

Repeated elemental analysis gave the same results. It is possible that 20 is always admixed with some 21.

ir : ν_{max} (KBr) cm^{-1}, 3420, 3060 (NH) , 1690 (C=O) 1630, 1600 (C=C, C=N).

XXII. Hydrolysis of the bis-salt 20: Preparation of the monosalt 21:

A suspension of the bis-salt 20 (1.2 g, 1.93 mmol) in water (90 ml) was left immersed in boiling water for 0.25 hours, cooled, filtered and crystallized from MeOH to

give 0.96 g (92%) of the mono-salt 21; colourless needles, mp. 225-228°C.

Anal. Cald. for $C_{28}H_{24}N_5O_2Br$ (Mol. Wt. 542)
C, 61.9; H, 4.4; N, 12.9%

Found: C, 62.0; H, 4.2; N, 12.9%

ir : ν_{max}(KBr) cm^{-1}, 3460, 3020 (amide), 1710 (C=O), 1660, 1600 (C = C, C=N)

^{1}H nmr: δ(DMSO-d_6) 200 MHz: 5.05 (s, 2H, -C$\underline{H}_2$COPh), 5.7 (s, 2H, -C$\underline{H}_2$Ph), 6.4-7.1 (m, 16H, phenyl), 7.35 (d, J = 8H_2, 2H, -NHC$\underline{H}_2$COPh), 7.91 (s, 1H, 6-purine proton), 8.75 (s, 1H, 2-purine proton)

^{13}C nmr: δ(DMSO-d_6); 190.8 (carbonyl), 145.5, 136.0, 134.7, 134.5, 133.9, 133.8, 131.6, 129.1, 128.9, 128.7, 128.3, 125.6, 114.1, 109.59, 55.7 (-CH_2), 49.1 (-CH_2).

XXIII. The reaction of the bis-alkylated mono-salt 21 with benzyl amine: Isolation of the key enamine intermediate 22 and daughter product 1-benzyl 5-phenyl imidazole (8):

A mixture of 21 (0.9 g, 1.66 mmol), benzylamine (1.2 ml, 11.2 mmol) and dry xylene (30 ml) was refluxed for 4 hours, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc::65:35 gave 0.25 g (28%) of the

enamine 22; colourless crystals, mp. 136-138°C.

tlc : 100% EtOAc; Rf. 0.7

Anal. Cald. for $C_{34}H_{30}N_6$ (Mol. Wt. 522)

C, 78.16; H, 5.74

Found : C, 78.2; H, 5.43

ir : ν_{max}(KBr) cm^{-1}, 3240 (amide)

1630 (CO)

nmr : δ($CDCl_3$), 60 MHz : 3.7 (m, 2H, -NH-C<u>H</u>$_2$Ph, +D_2O, q), 4.22 (s, 2H, =N-C<u>H</u>$_2$Ph), 4.75 (s, 1H, -C<u>H</u>-C(NH)Ph), 4.85 (s, 1H, -C<u>H</u>$_2$Ph), 5.2 (m, 1H, N<u>H</u>, exch. with D_2O), 7.2-8.0 (m, 23H, aromatic)

m/z : 522 (M^+).

Further elution with PhH:EtOAc::55:45 gave 0.153 g (38%) of the derived product 8, mp 111°C.

XXIV. <u>The reaction of 22 with benzylamine: Demonstration of the intermediacy of 22 in the formation of the daughter product 8</u>:

A mixture of 22 (0.25 g, 0.478 mmol), benzylamine (0.2 g, 1.9 mmol), anhyd. p-TsOH (0.108 g, 0.57 mmol) and dry xylene (30 ml) was refluxed for 6 hours, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc::60:40 gave 0.098 g (88%) of the derived product 1-benzyl 5-phenyl

imidazole (8), mp. 110-111°C.

XXV. The reaction of 21 with benzyl amine and p-TsOH: The direct transformation to the derived imidazole 8:

A mixture of 21 (0.238 g, 0.45 mmol), benzylamine (0.2 g, 1.8 mmol), anhyd. p-TsOH (0.17 g, 0.9 mmol) and dry xylene (20 ml) was refluxed for 12 hours, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc::60:40 gave 0.07 g (72%) of the derived imidazole 8, mp. 111°C.

XXVI. The reaction of 21 with cyclohexylamine and p-TsOH: Isolation of the derived product 1-cyclohexyl 5-phenyl imidazole (14):

A mixture of 21 (0.450 g, 0.83 mmol), cyclohexylamine (0.520 g, 5.25 mmol), anhyd. p-TsOH (0.300 g, 1.57 mmol) and dry xylene (30 ml) was refluxed for 18 hours, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc:: 70:30 gave 0.091 (49%) of 14, colourless thick liquid, bp. 180°/0.1 torr.

XXVII. 4-Amino quinazoline (23):

4-Chloroquinazoline:

A mixture of 4-quinazolone (4) (11 g, 75 mmol), PCl_5 (21 g, 100 mmol) and $POCl_3$ (80 ml) was refluxed for 2 hours, evaporated, admixed with CH_2Cl_2 (100 ml), poured onto crushed

ice (~ 200 g), adjusted to pH ~ 8 with aqueous ammonia, extracted with CH_2Cl_2 (2 x 50 ml), dried, evaporated, dissolved in benzene, passed through a short column of alumina and eluted with PhH:EtOAc ::6·1 to yield 10 gm (81%) of 4-chloroquinazoline, mp. 97°C (lit.[31] mp 97°C).

4-Phenoxy quinazoline:

4-Chloroquinazoline (5 g, 30.3 mmol) was added to a solution of potassium phenoxide (35 mmol) in phenol (60 g), held at 70°C for 1.5 hours, cooled, cautiously admixed with aqueous 2N NaOH(50 ml), extracted with ether (3 x 50 ml), washed with 2NNaOH (4 x 60 ml), dried, evaporated and the residue on crystallization from hot hexane gave 4.8 g (71%) of 4-phenoxy quinazoline, mp. 76-77°C (lit.[32] mp 77°C).

4-Amino quinazoline (23):

4-Phenoxy quinazoline (4.8 g, 22 mmol) was added to NH_4OAc (24 g) held at fusion (160°C), the mixture heated at 190°C for 0.1 hour, cooled, admixed with water (10 ml), adjusted to pH ~ 10, with 2N NaOH(~ 50 ml), filtered and the residue on crystallization from hot methanol gave 2.3 g (74%) of 23mp265-266°C (lit.[32] mp. 266°C).

XXVIII. The alkylation of 4-amino quinazoline (23) with phenacyl bromide: Isolation of 3N-alkylated salt 24:

The reaction of 23 (1.45 g, 10 mmol) with phenacyl bromide (3 g, 15 mmol) when carried out precisely as described for 9-benzyl adenine (19) (Experiment XXI) gave 2.3 g (68%) of 24; colourless crystals, mp 283-288°C.

Anal. Cald. for $C_{16}H_{14}N_3OBr$ (Mol. Wt. 344)
C, 55.8; H, 4.07; N, 12.20%

Found: C, 55.9; H, 3.78; N, 11.98%

ir : ν_{max}(KBr) cm^{-1}; 3360, 3260, 3060 (-NH), 1695, 1675 (CO)

nmr : δ(DMSO-d_6), 200 MHz: 5.5 (s, 2H, $-CH_2COPh$), 6.7-7.3 (m, 8H aromatic), 7.68 (d, J=8 Hz, 1H), 8.0 (s, 1H, 2-quinazolyl proton).

XXIX. The reaction of 24 with hot water: Isolation of 25 arising from Dimroth rearrangement:

The treatment of the salt 24 (1.7 g, 5 mmol) with hot water (100 ml) precisely as described in Experiment XXII gave 1.3 g (77%) of the Dimroth rearrangement product 25; white needles, mp. 306-311°C.

Anal. Cald. for $C_{16}H_{14}N_3OBr$ (Mol. Wt. 344)
C, 55.8; H, 4.07%

Found : C, 56.0; 3.99%

ir : ν_{max}(KBr) cm^{-1}, 3260,3060 (amide) 1690,1675 (amide carbonyl).

m/z : 263 (M^+ − HBr).

XXX. The reaction of salt 25 with benzyl amine and p-TsOH: The isolation of 4-benzylamino quinazoline (26):

The reaction of 25 (0.44 g, 1.28 mmol) with benzylamine (0.716 g, 6.69 mmol) and anhyd. p-TsOH (1 g, 6.26 mmol) in dry xylene (30 ml) when carried out exactly as described in Experiment XXV gave 0.172 g (56%) of 26, mp 172-173°C

tlc : PhH:EtOAc::50:50; Rf. 0.7

Anal. Cald. for $C_{15}H_{13}N_3$ (Mol. Wt. 235)

C, 76.6; H, 5.5; N, 17.8%

Found : C, 76.4; H, 5.32; N, 17.51%

ir : ν_{max}(KBr) cm^{-1}, 3240 (amide) 1615 (C=C)

nmr : δ($CDCl_3$), 60 MHz: 4.87 (d, +D_2O, s, 2H, -NHC$\underline{H}_2$Ph) 6.47 (br, 1H, -N$\underline{H}$), 7.12-7.97 (m, 9H, aromatic), 8.64 (s,1H,quinazolyl proton).

m/z : 235 (M^+).

XXXI. 4-Benzylamino quinazoline (26):

A stirred solution of 4-chloroquinazoline (0.49 g, 3 mmol) in dry benzene (50 ml) was admixed with benzylamine

(0.481 g, 4.5 mmol), the mixture left stirred at rt. for 12 hours, evaporated and chromatographed on silica gel. Elution with PhH:EtOAc::65:35 gave 0.29 g (49%) of 26, mp. 172-173°C (lit.[33] mp 172°C).

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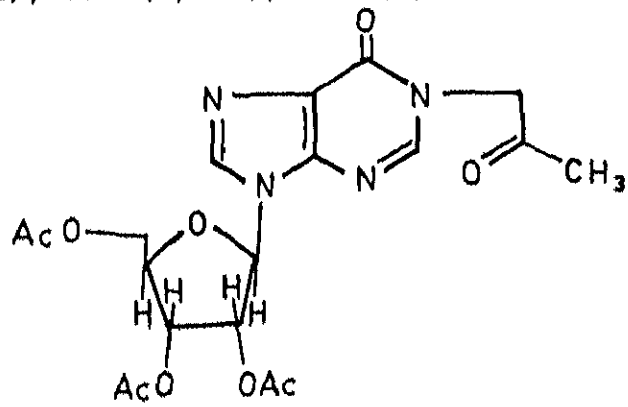
17. In the course of exploratory studies, the readily available inosine triacetate was alkylated by the usual procedure with bromoacetone [43, mp 67°C, Yield 40%, ir: ν_{max} (KBr) cm^{-1}, 1740 (C=O), 1690 (amide carbonyl); nmr: $\delta(CDCl_3)$, 60 MHz: 2.1 (s, 9H, $-OCOCH_3$), 2.3 (s, 3H, $-COCH_3$), 4.4 (s, 2H, $-CH_2OCOCH_3$), 4.9 (s, 2H, $-CH_2COCH_3$), 5.6 (br, 1H), 6.0 (m, 2H), 8.0 (s, 2H, aromatic).



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The reaction of 43 with 4 equivalents of benzylamine and 2 equivalents of p-TsOH in refluxing xylene for 10 hours, conditions generally employed in the earlier cyclic processes, yielded none of the derived product , namely, 1-benzyl 5-methyl imidazole (9).

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19. Compound 22 on reflux in xylene with only p-TsOH failed to give the derived imidazole.

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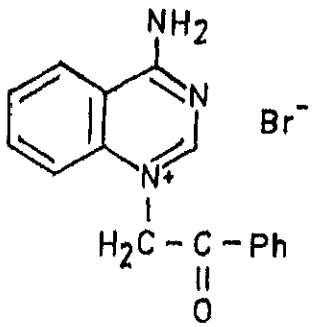
22. 4 Amino quinazoline offers three sites for alkylation with $PhCOCH_2Br$. Compound 24 and 25 represent two of the possibilities. Interestingly, alkylation at the third site, namely, N-1 was observed when 23 was either treated with 1.5 equivalents of the reagent in DMF at rt. for 8 days, or with 4 equivalents under the same conditions for 2 days. Yield 48%, mp 310°C.



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Anal. Cald. for $C_{16}H_{13}N_3OBr$ (Mol. Wt. 343)

C, 55.8; H, 4.07; N, 12.20%

Found : C, 55.68; H, 3.84; N, 12.65%

ir : ν_{max}(KBr) cm^{-1}; 3360, 3250 (-NH), 1685, 1665, 1610

nmr : δ(DMSO-d_6), 200 MHz : 5.5 (s, 2H, $C\underline{H}_2$), 6.7-7.3 (m, 8H, aromatic), 7.7 (d, J = 8 Hz, 1H), 8.03 (s, 1H)

^{13}C nmr : δ(DMSO-d_6) : 191.8 (carbonyl), 163.2, 154.8, 138.7, 136.8, 134.5, 133.76, 128.96, 128.4, 125.7, 117.9, 112.2, 56.7 ($-CH_2$).

m/z : 263 (M^+ - HBr).

23. The numbers for compounds in this sub-section are in continuation of those cited in Part I and Part II of the thesis.

24. Please see ref.48 of the background.

25. Please see ref. 105 of the background.

26. Please see ref. 95 of the background.

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CHAPTER II

COMPETING PATHWAYS IN TEMPLATE SYNTHESIS : ALKALI MEDIATED RING-RING TRANSFORMATIONS IN 4-QUINAZOLONES

II. A. INTRODUCTION

An important step in the ATP-Imidazole cycle is the hydrolytic cleavage of an alkylated adenine, resulting in the regeneration of the template amide grouping. A similar pathway with the model system, 3-substituted 4-quinazolones, would result in the hydrolytic rupture of the 3,4-bond. However, all such endeavours, which is the focus of the work cited in this part, did not succeed. Nevertheless, these studies are noteworthy in that they have led to the demonstration of subtle, interesting and novel properties of these compounds.

Every attempt to effect the hydrolytic cleavage of the 3,4-bond of a range of 3-substituted 4-quinazolones invariably led to products arising from 2,3-bond cleavage and loss of elements of formic acid. To steer the system from proclivity

from 2,3 cleavage, the 2-blocked compound , 2-methyl 3 phenacyl 4-quinazolone was prepared. The action of dilute alkali on this compound, gave, in quantitative yields, a novel aromatic tricyclic system, demonstrating that this reaction is entirely controlled by the conjugate base of the 2-methyl grouping, thus effectively precluding the 1,2 and 3,4 -bond cleavage as well as intramolecular enolate addition. In sharp contrast, this propensity was entirely curbed with 2-methyl 3-benzamido 4-quinazolone which on treatment with dilute alkali gave only the triazole arising from the expected 3,4-bond cleavage and the unwanted subsequent cyclization involving the 1N position. The latter tendency could not be overcome with 2-phenyl 3-benzamido 4-quinazolone which again gave, on reaction with dilute alkali, the triazole. 2-Phenyl 3-benzamido 4-quinazolone underwent hydrolytic cleavage in distilled water at 200°C leading to a multitude of products arising from 3,4-bond cleavage. All these products have been characterized and their formation explained.

Heterocyclic systems possessing two or more nitrogens in the ring are usually prone to attack by hydroxide ions. Not infrequently, such reactions lead to products where the parent ring gets ruptured and a new ring gets formed. These are quite interesting transformations in reaction mechanisms

and a very brief account of this aspect is presented as an appropriate background (SECTION II.B) for the work that is described in the following section (SECTION II.C).

II. B. BACKGROUND

As stated in the introduction (SECTION II.A), heterocyclic ring systems carrying two or more nitrogens are susceptible to aqueous hydroxide. Such processes lead not infrequently, to ring-ring transformations, a pathway in which a new ring is formed at the expense of the parent. This aspect has been highlighted in the book entitled, 'RING TRANSFORMATIONS OF HETEROCYCLES'. The purpose of this section is merely to add, to the exhaustive information cited in the book, few examples that are considered representative and which have aspects that are similar to that encountered in the present work (SECTION II.C).

3-Propargyl 4-quinazolone (IV)[2] on treatment with NaOEt followed by NaOH leads to the formation of oxazole V (CHART II.B.1). The most interesting aspect of this transformation is that the overall change here involves cyclization to the 4-oxogrouping of the parent IV, a pathway that has not been encountered in the present work. The overall change is envisaged *via* a key allenic intermediate arising from the isomerization of IV with NaOEt[3] (CHART II.B.1).

In CHART II.B.2 is presented the transformation of a bicyclic 1,2,4-triazole (VI) to the isomeric 1,2,4-triazole

CHART II.B.1

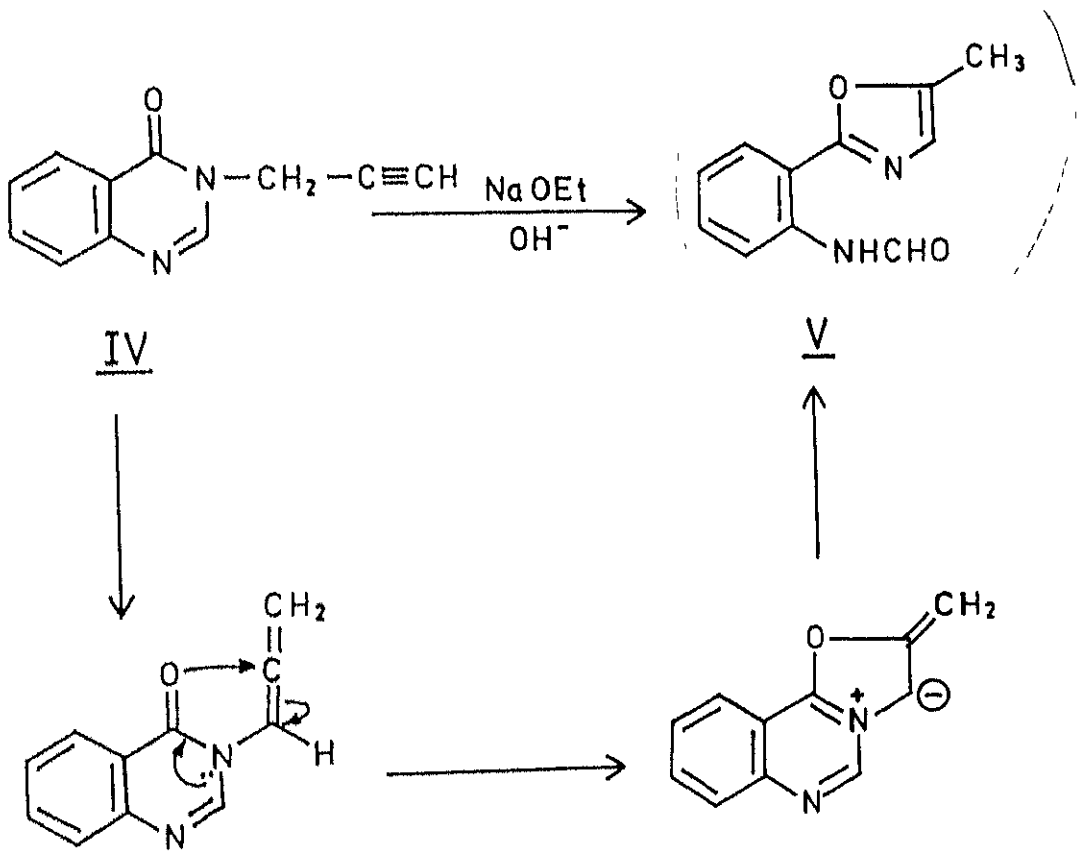
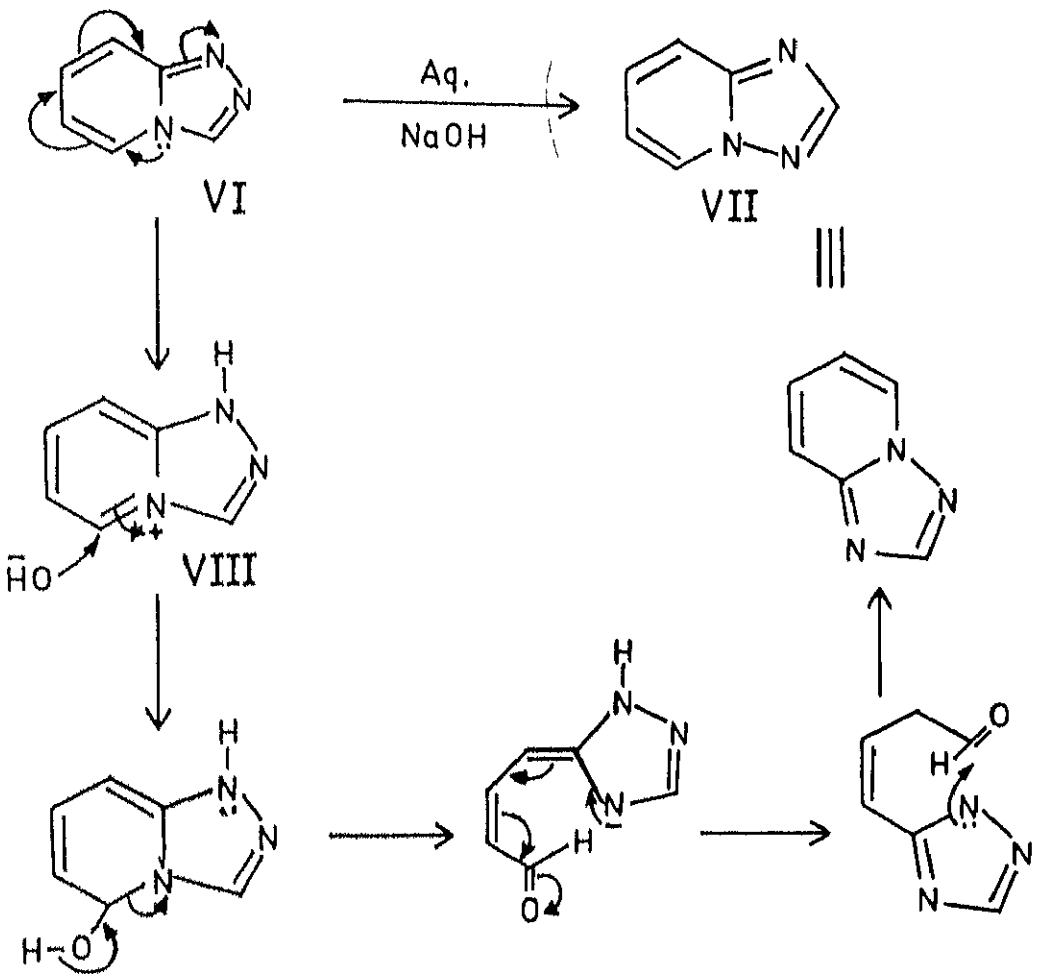


CHART II.B.2



(VII) on treatment with aqueous NaOH. The overall transformation apparently involves a shuffling of the nitrogens. In reality, however, the reaction proceeds *via* ring opening, initiated by the protonated intermediate VIII followed by recyclization[4].

The transformation of 6-chloro 1,4,5-triazanaphthalene (IX) to 4-azabenzimidazole (X), brought about with $NaNH_2$ in liquid NH_3, represents a complex skeletal reorganization and demonstrates the relative instability of multiple nitrogen containing 6-membered rings compared to pyridine (CHART II.B.3). The IX → X change can be understood in terms of a series of intermediates eventually leading to X with extrusion of elements of HCN and chloride ion. Although this illustration uses bases stronger than hydroxide, it is, nevertheless, chosen as a good example of ring-ring transformation[5].

An interesting ring-ring transformation is represented in the XI → XII (CHART II.B.4). The change can be readily understood in terms of hydroxide mediated imine hydrolysis followed by recyclization[6].

The examples thus far cited involve hydroxide as nucleophile. The XIII → XIV change illustrated in CHART II.B.5 represents a fascinating ring-ring transformation initiated by hydroxide as a base. The overall change can be

CHART II.B.3

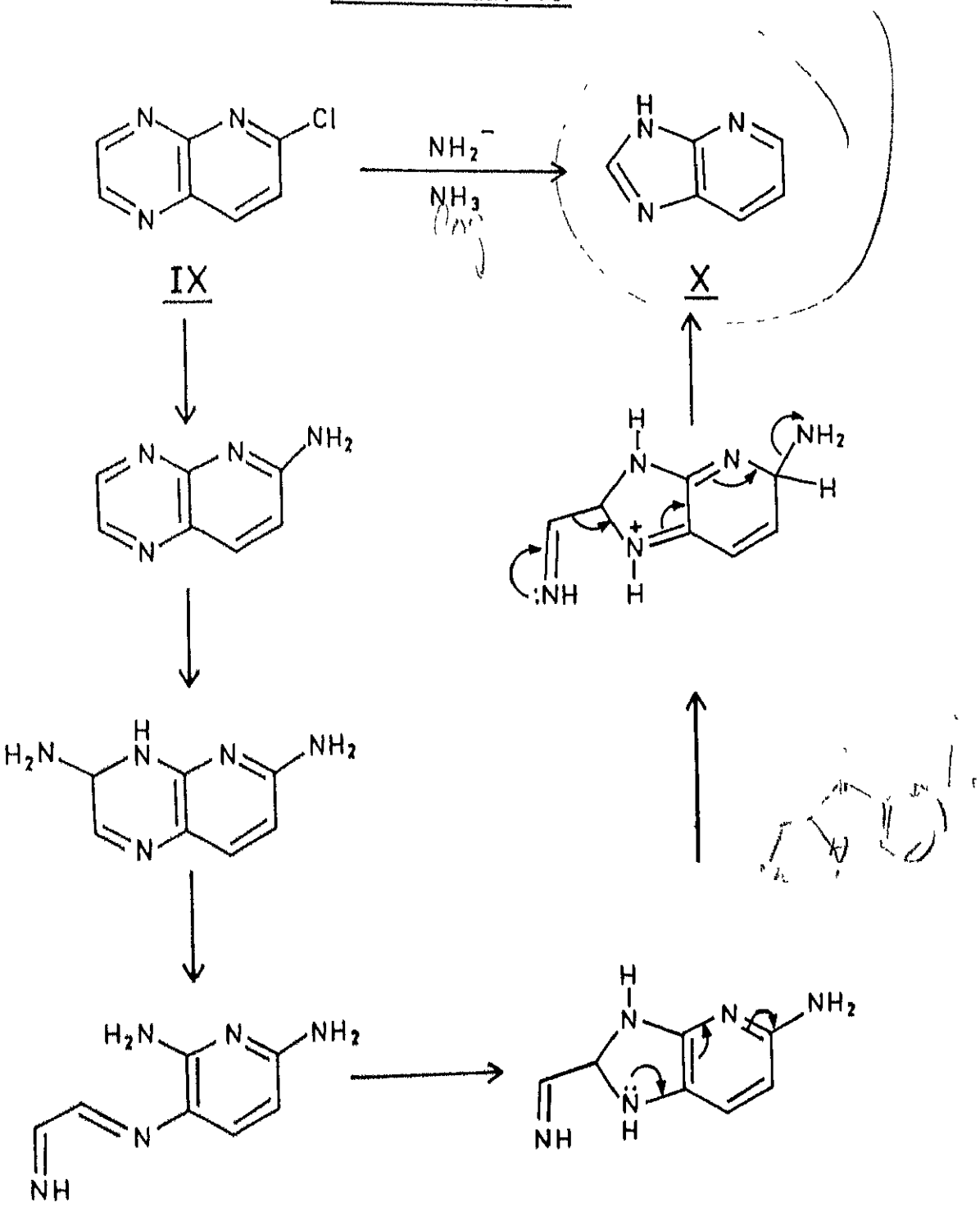


CHART II.B.4

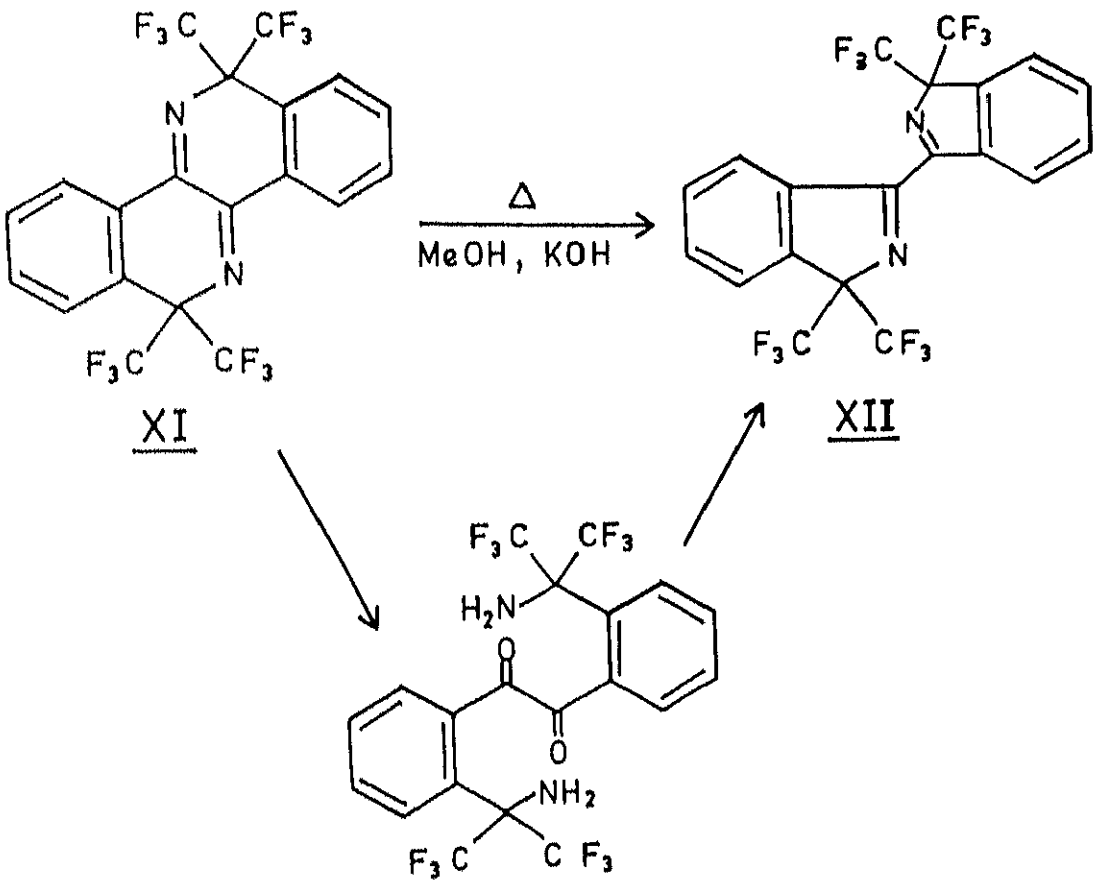
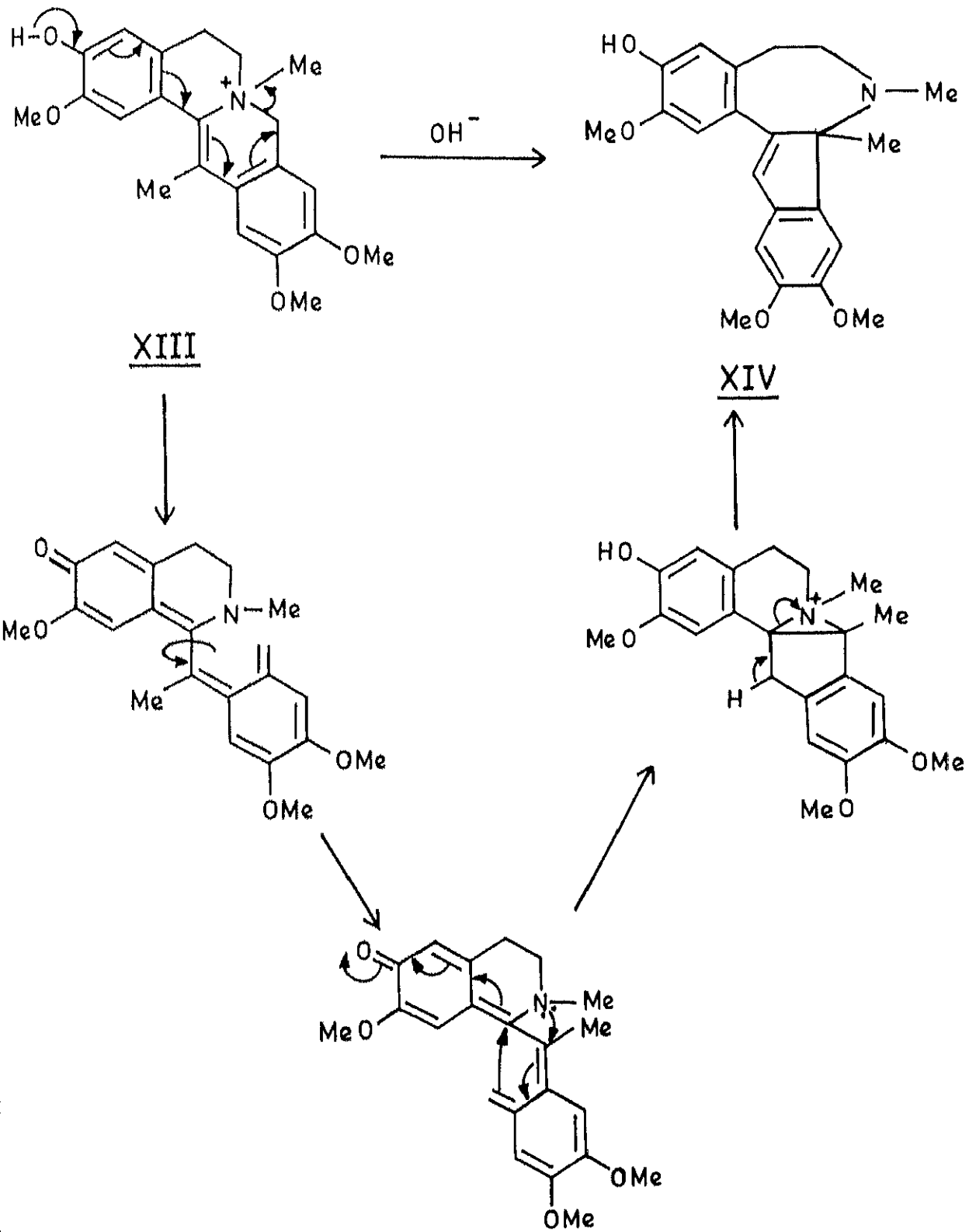

F3C
CF3
N
N
F3C
CF3
XI
Δ
MeOH, KOH
F3C
CF3
N
N
F3C
CF3
XII
F3C
CF3
H2N
O
O
NH2
F3C
C F3

CHART II.B.5

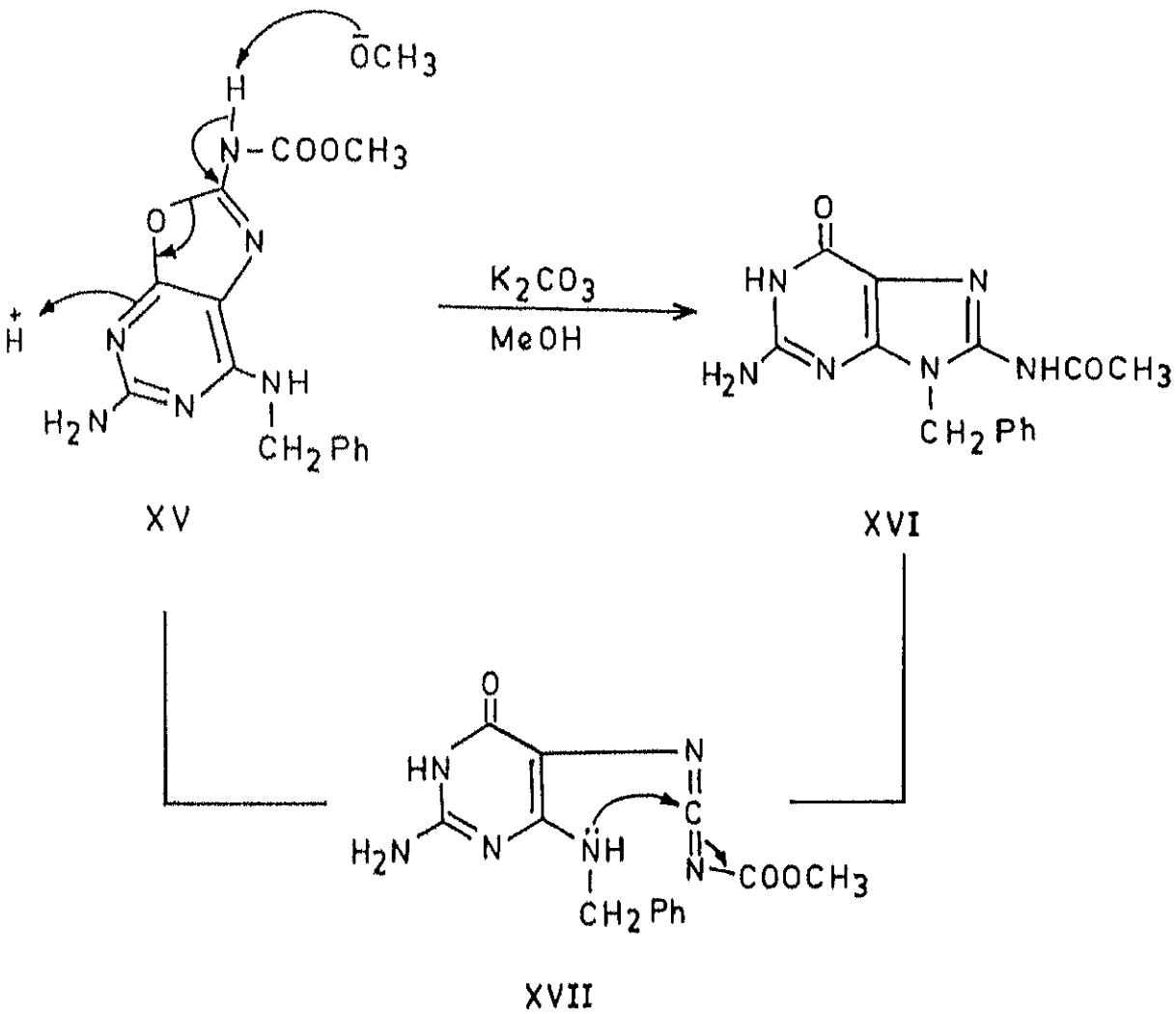

H-O
MeO
Me
N
Me
Me
OMe
OMe
OH⁻
HO
MeO
N
Me
Me
MeO
OMe
XIII
XIV
O
MeO
N
Me
Me
OMe
OMe
HO
MeO
Me
N
Me
H
OMe
MeO
O
MeO
N
Me
Me
OMe
OMe

understood in terms of the conjugate base of XIII initiating a fragmentation reaction, whose driving force is the neutralization of the charged nitrogen[7].

An interesting ring-ring transformation, reported recently[8], is the base promoted oxazole → imidazole change involving XV. This reaction which results in the formation of guanine XVI is noteworthy in the sense that the common intermediate XVII prefers addition involving the nitrogen functionality (CHART II.B.6).

An aspect that is latent but nevertheless important is the use of such ring-ring transformations in the design of synthetic strategies.

CHART II.B.6



XV

XVI

XVII

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II.C. PRESENT WORK

The preceding part describes the development of appropriate experimental strategies leading to the chemical simulation of the ATP-Imidazole cycle. As outlined there, the model template anthranilamide played a pivotal role in these studies. The realization of the first step of the cycle, namely, the incorporation of the elements of formic acid as well as that of the second step involving specific alkylation was easily achieved on this model leading to a series of specifically 3-substituted 4-quinazolones. However, all endeavours to bring about the hydrolytic opening of the 4-oxo grouping resulting in the 3,4-bond cleavage - a process that is similar to that of the Natural cycle (CHART I.C.1) - did not succeed. Nevertheless these studies, outlined below, are noteworthy in that they not only demonstrated novel transformations of 4-quinazolones but also provided a fuller perspective of diverse requisites associated with the bond re-organization of the ATP-Imidazole cycle.

The compounds pertinent to this study are 3-acyl alkylated 4-quinazolones, which easily provided derived products with amines (PART I) and 3-acyl amido 4-quinazolones. At the outset, it was envisaged that these systems would suffer hydrolytic cleavage of the 3,4-bond on treatment with dilute

alkali and the resulting open chain systems could undergo cyclization and cleavage, akin to the events of the Natural ATP Imidazole cycle, leading to, respectively, oxazoles and oxadiazoles, as derived products, regenerating the template anthranilic acid (CHART II.C.1 : Path A). Parenthetically, Path B represents the successful simulation studies outlined in the earlier part.

The reaction of 3-phenacyl 4-quinazolone (6)[1] in refluxing 0.6 N aqueous NaOH gave a 45% yield of anthranilic acid (45), but none of the expected derived product, 5-phenyl oxazole. Instead, there was obtained, in 37% yields, 3-amino, 2,4-diphenyl pyrrole (46), mp 180-181°C (lit.[2] mp. 178-179°C). The structural assignment for 46 is supported by spectral data.

---

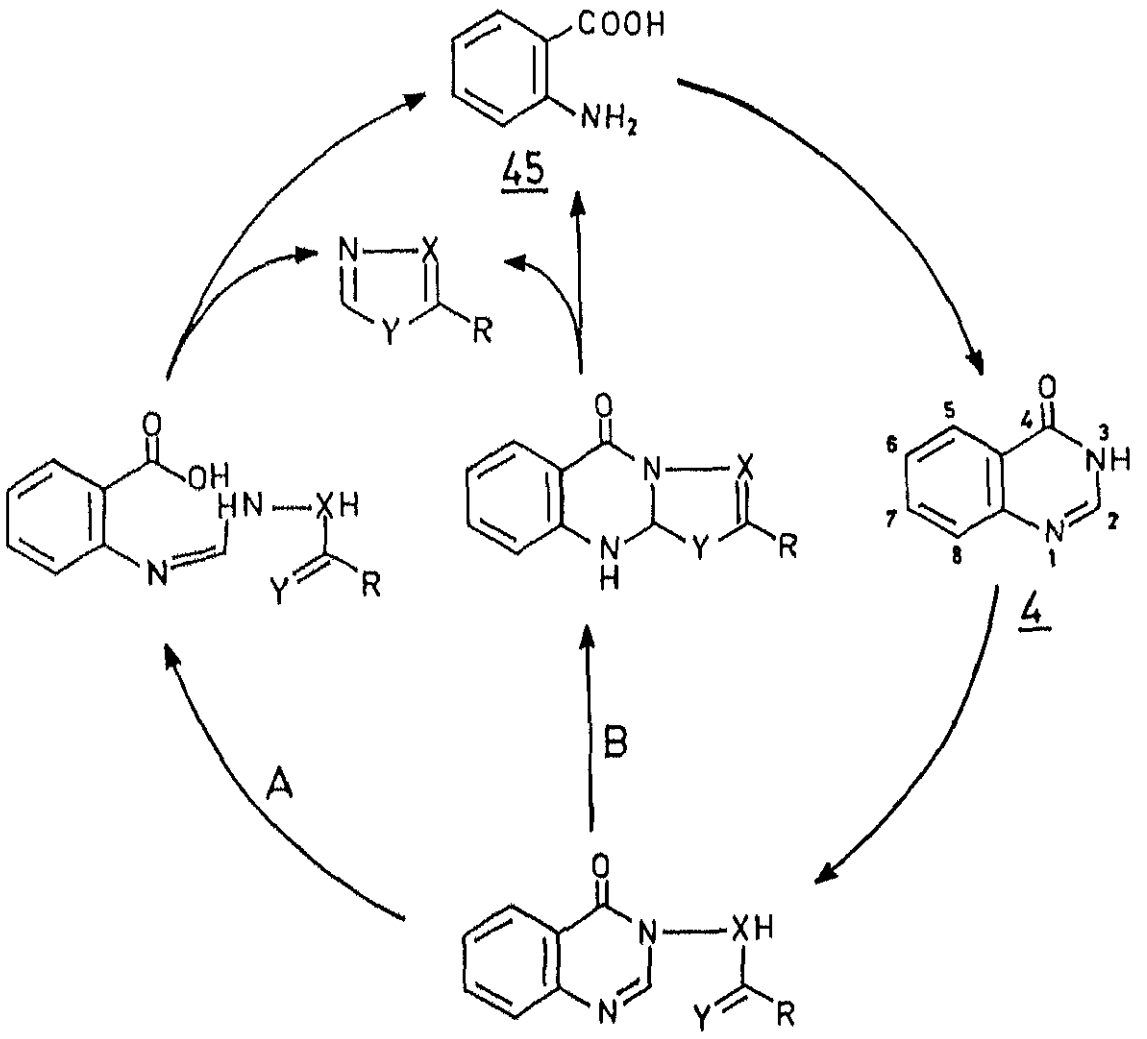
46 mp : 180-181°C (lit.[2] mp 178-179°C)

ir : ν_{max} (KBr) cm^{-1}; 3430, 3240 ($-NH_2$, NH), 1615 (C=C).

nmr : δ ($CDCl_3$), 60 MHz: 3.67 (br, 2H, $-N\underline{H}_2$, exch.D_2O), 6.6 (d, J = 3Hz, 1H, 5-pyrrole proton), 6.87-8.1 (m, 11H, -N<u>H</u> and aromatic)

m/z : 234 (M^+).

CHART II.C.1



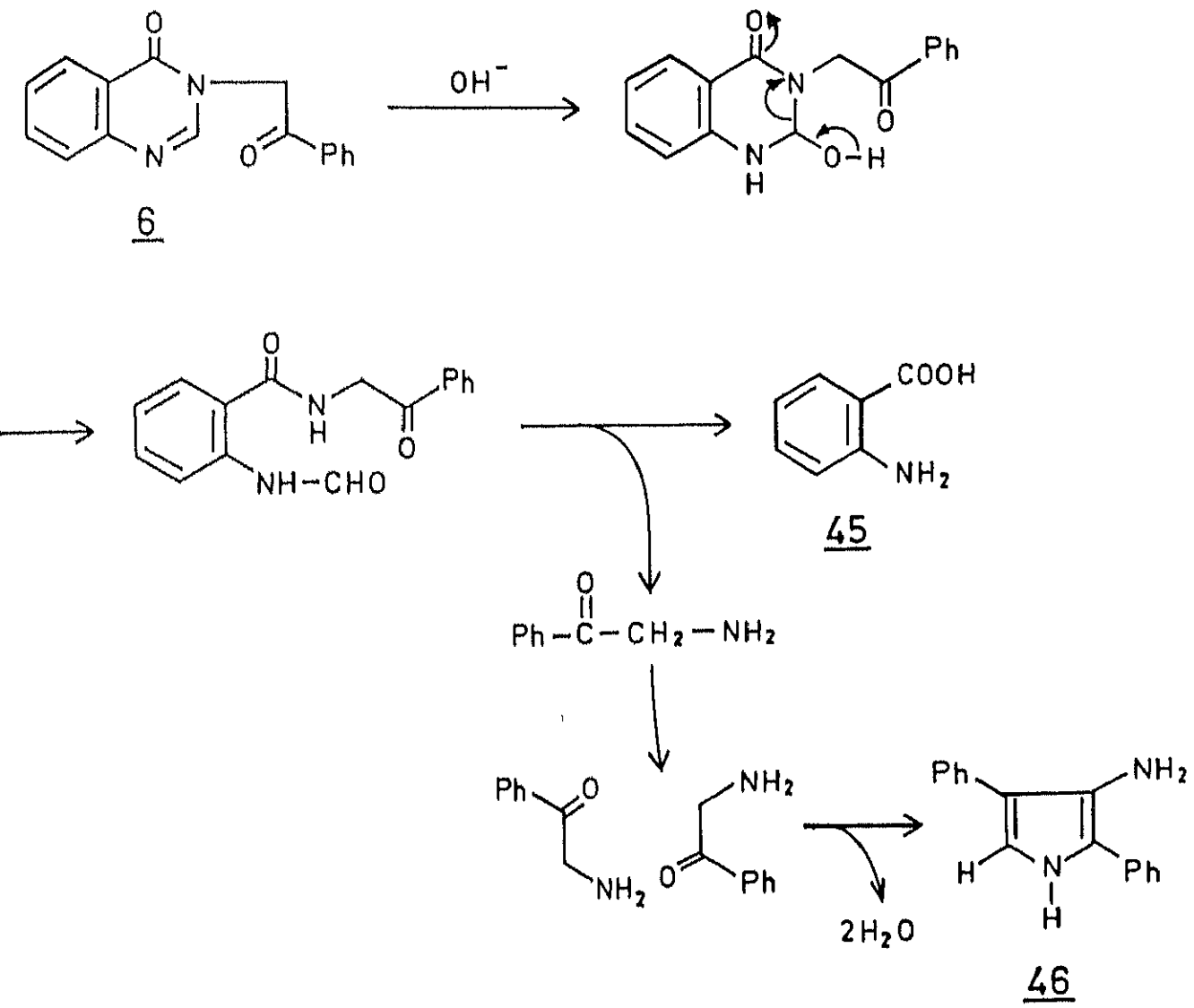
6: XH = CH_2, Y = O, R = Ph

49: XH = NH, Y = O, R = Ph

The formation of compound 46, rationalized in CHART II.C.2, reflects the importance of addition of elements of hydroxide ion to the 1,2-bond of 6, over the anticipated enolate addition, that would have led to derived products. This adduct opens, rupturing the ring and the resulting formamide intermediate undergoes complete hydrolysis to anthranilic acid, formic acid and ω-amino acetophenone. The latter on dimerization and loss of water would give the pyrrole 46.

Support for the proposed sequence in the cleavage of 6 with dilute alkali has been obtained by studies on model systems. The reaction of a variety of 3-substituted 4-quinazolones with organometallic reagents - in the place of dilute alkali - gave invariably products arising from the addition of the nucleophilic reagent to the 2-position of the system. In this study, the adducts as well as products anticipated from the 2,3-bond rupture were isolated[3]. Thus, the sequence of events envisaged in CHART II. C.2 is supported by ancillary evidence. Additionally, direct evidence of the loss of the 2-carbon as formic acid has been obtained by examination of several 3-substituted 4-quinazolones with dilute alkali, under conditions used for the 6 → 45 → 46 change. Thus, the reaction of 3-allyl 4-quinazolone (47) with dilute alkali gave, in addition to anthranilic acid (45), its N-allylamide 48, which clearly shows that the cleavage of the

CHART II.C.2



3,4-bond would be the last step under these reaction conditions. The preference for the hydrolytic cleavage of the 2,3 over 3,4-bond is also shown in the case of 3-benzamido 4-quinazolone (49) - a potential precursor for the derived product 2-phenyl 1,3,4-oxadiazole (CHART II.C.1). The reaction of 49 with refluxing 2N NaOH gave anthranilbenzhydrazide (50) - arising from the cleavage of the 2,3-bond and loss of formic acid and products of further hydrolysis[3] (CHART II.C.3)

In view of the demonstrated propensity of hydroxide ion to add to the 1,2-bond of quinazolones over any other process, it was anticipated that the blocking of the 2-position with substituents would reverse the tendency and at the same time promote alternate pathways that are part of the anticipated template cycle (CHART I.C.1). With this objective several 2-blocked 3-substituted 4-quinazolones were prepared and their reactions with dilute alkali studied. Indeed, in these cases where additional complications were not present, this strategy resulted in the cleavage of the desired 3,4-bond.

2-Methyl 4-quinazolone (36) was prepared from acetanthranil and NH_4OAc.

36: mp : 230°C (lit.[4] mp. 233°C)

ir : ν_{max}(KBr) cm^{-1}: 3400, 2860 (-NH), 1670 (-CO)

CHART II.C.3

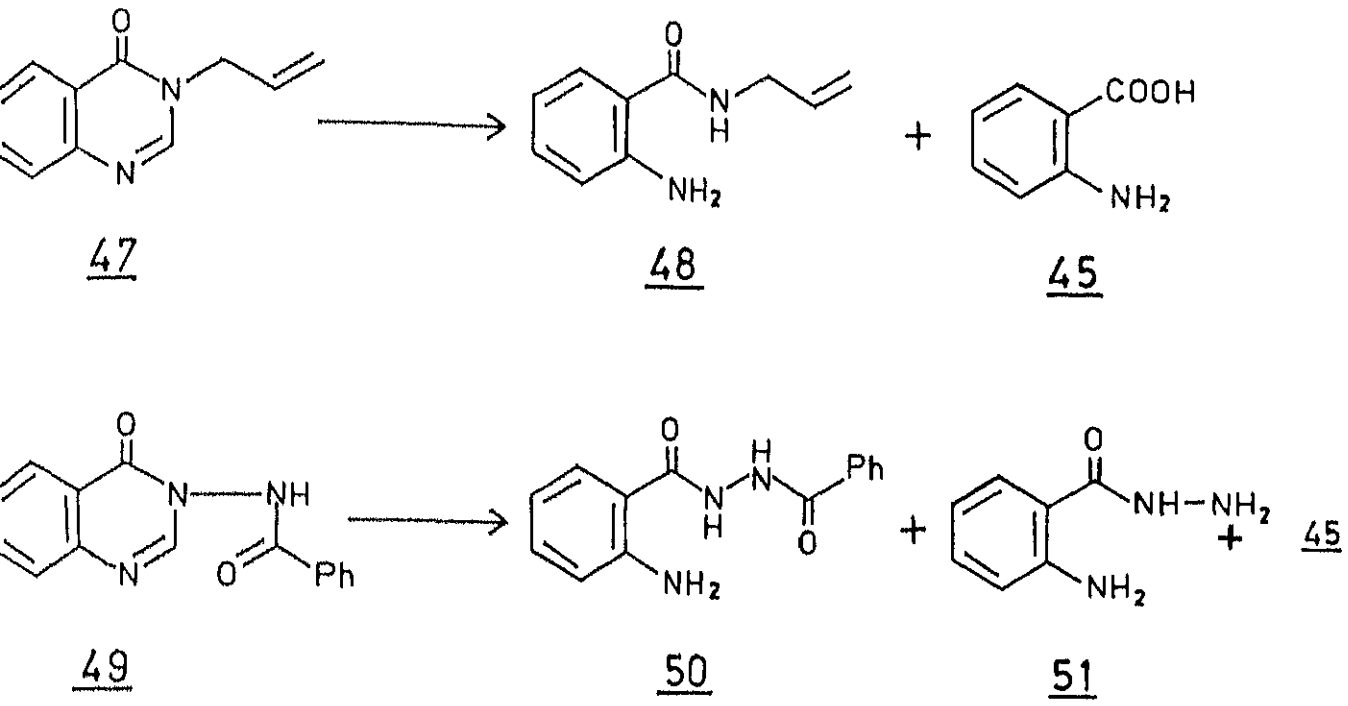
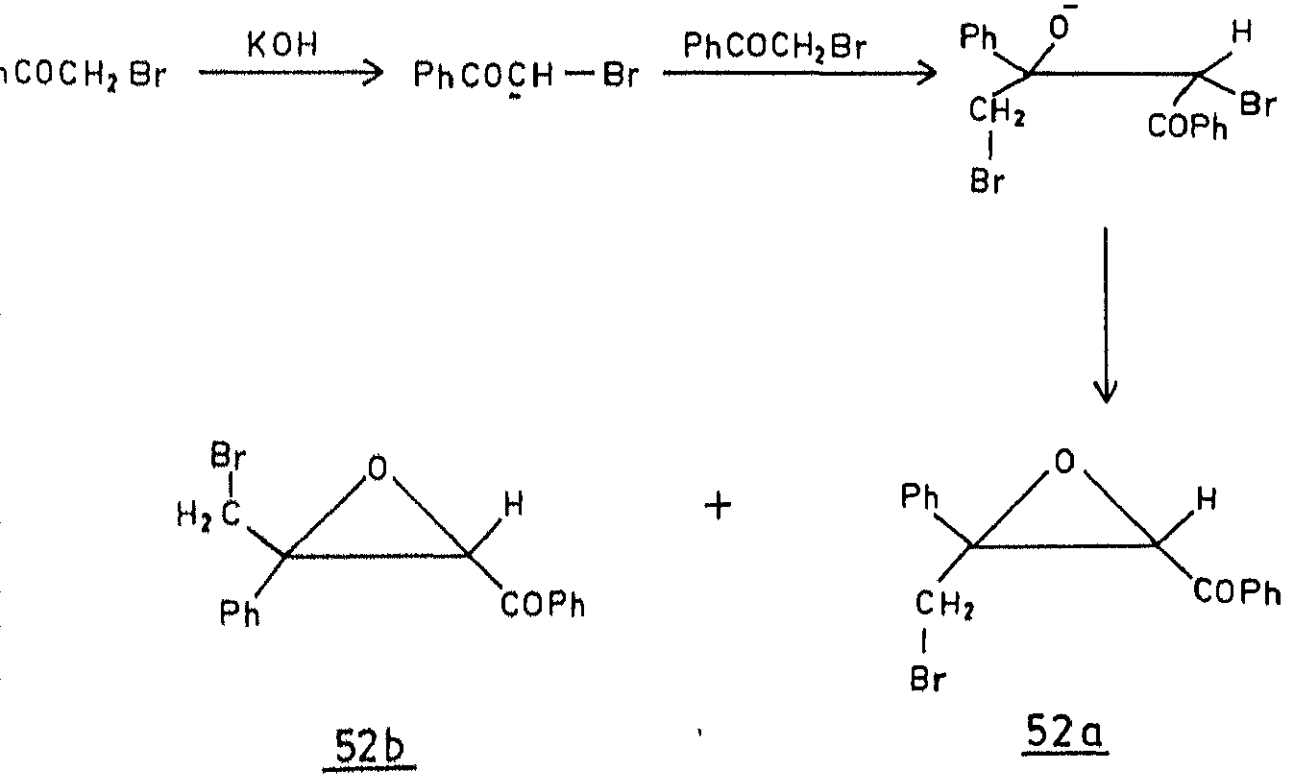


CHART II.C.4



The apparently straightforward preparation of 2-methyl 3-phenacyl 4-quinazolone 38, by the reported procedure[5], involving alkylation of the conjugate base of 36 with phenacyl bromide, was, in the event, beset with unexpected complications. The reaction gave a compound, mp. 135-136°C, in agreement with that reported for 38 and a more polar compound, mp. 164°C. Surprisingly, inspite of the fact that the mp. 135-136°C obtained for one of the products matched with mp. 135°C reported for the expected 2-methyl 3-phenacyl 4-quinazolone (38), its nmr spectrum revealed the absence of any $-CH_3$ function and therefore ruled out structure 38 for this compound. On the other hand, the higher melting compound, mp. 162°C had spectral and analytical properties in complete agreement with the desired compound 38. The yield of this compound was 24%.

---

38 mp : 164°C

ir : ν_{max} (KBr) cm^{-1}; 1670 (CO),

nmr : δ ($CDCl_3$), 60 MHz: 2.46 (s, 3H, $-C\underline{H}_3$), 5.39 (s, 2H, $-C\underline{H}_2COPh$), 7.26-8.36 (m, 9H, aromatic)

m/z : 278 (M^+).

Thus, the nature of the compound, mp 135-136°C had to be determined. The nmr spectrum of this compound tended to show that it was a mixture of products, although it exhibited homogeneity in tlc. The general spectral properties of this compound indicated that it must have arisen from phenacyl bromide alone. This conclusion was soon confirmed by a blank reaction involving the treatment of phenacyl bromide with dilute alkali, leading to isolation of a substance having a similar melting point and spectral properties. The lack of purity evident from the nmr coupled with its apparent homogeneity in tlc suggested that compound mp 135-136°C was a mixture of isomers. This assumption was proved correct on treatment of compound mp. 135-136°C with hot dilute alkali which led to isolation of compound mp 162°C, whose clean nmr spectrum coupled with other spectral and analytical properties led to the assignment of structure 52b. This clarification, inturn, led to the characterization of compound mp 135-136°C as a mixture of isomers, 52a and 52b in the ratio of 1:4. The structural assignments for 52a and 52b were greatly facilitated from studies reported in the literature[6], on the products arising from the self condensation of phenacyl bromide in the presence of alkali. However, in

the literature, the compound mp 135-136°C was considered as a pure isomer and was designated as α whilst compound 162°C was designated as β. The nmr spectra and analysis of these compounds in the present work clearly shows that the α-form is a mixture. Thus, whilst the pure β, 52b is available the pure α, 52a is not known. Excepting for this small discrepancy the structural assignments provided in the literature matches with the conclusions arrived at in the present work. Finally, the yield of 52a + 52b, mp 135-136°C encountered during alkylation was 21%.

52a + 52b: mp : 135°C

ir : ν_{max} (KBr) cm^{-1}; 1665 (-CO)

nmr : δ($CDCl_3$), 60 MHz: 52a + 52b ::1:4,
3.8 (dd, 52a), 3.9 (d, 52b), 4.4 (s, 52a),
4.6 (s, 52b), 7.4 (m, aromatic)

52b : mp : 162°C

nmr : δ($CDCl_3$), 60 MHz: 3.9 (d, 2H, $-C\underline{H}_2Br$),
4.6 (s, 1H, $-C\underline{H}COPh$), 7.3-8.2 (m, 10H,
aromatic)

As analyzed by earlier workers[6], the formation of 52a + 52b could be readily understood on the basis of a base promoted Darzen type condensation of phenacyl bromide

(CHART II.C 4).

The reaction of 2-methyl 3-phenacyl 4-quinazolone (38) with dilute alkali under conditions similar to that used for 6 gave compound, mp. 205-206°C, which has been assigned structure 53, on the basis of spectral data. The yield of 53 was 97%.

---

53 : mp : 205-206°C

ir : ν_{max} (KBr) cm^{-1}, 1665 (-CO)

nmr : δ ($CDCl_3$), 60 MHz : 5.05 (d, J = 0.5 Hz, 2H, allylic coupling), 6.9 (t, J = 0.5 Hz, 1H), 7.3-8.4 (m, 9H)

m/z : 260 (M^+).

As anticipated of the structure 53, it readily underwent aromatization, even on attempted crystallization, in quantitative yields, giving rise to 54 (mp. 185°C) whose structural assignment is again fully supported by spectral data.

---

54 : mp : 185°C

ir : ν_{max} (KBr) cm^{-1}; 3400 (br, -NH), 1660 (-CO)

nmr : δ ($CDCl_3$), 60 MHz : 7.26-8.44 (m, aromatic)

m/z : 260 (M^+).

The formation of 53 and 54 could be rationalized on the basis of transannular cyclization involving the conjugate base arising from the 2-substituent (CHART II.C.5).

Although 2-methyl 3-substituted 4-quinazolones are known to form conjugate bases arising from the 2-substituent under similar conditions[7], the total control exhibited by this grouping in the 38 → 53 change is extremely surprising, particularly in the light of the fact that the 3-phenacyl ligand possesses an equally acidic $-CH_2$ function. Indeed, the conjugate base of this could have interacted with the 1,2-bond of 38, eventually leading to derived products (CHART II.C.1). In any event, the above experiment clearly showed that of the four possibilities available, namely, alkaline cleavage of either the 3,4 or 2,3-bond and reactions arising from the conjugate bases involving either the 3 or 2 substituent, the last pathway is overwhelmingly preferred. The present work has provided an excellent method for novel systems of the type 54 starting from simple precursors.

The clean 38 →53 transformation could mean the restrictive formation of the conjugate base of the methyl, substituent, thus providing a unique pathway for the change. To test this, compound 38 was stirred at rt. with 3 equivalents of NaH in DMSO for 24 hours. Surprisingly, work-up yielded essentially the starting material. Similar results were obtained even in refluxing dioxan. The NaH experiments can be understood on the basis of formation of extensive conjugate base formation involving the 3-ligand, which precludes

cyclizations involving the conjugate base of the 2-substituent.

The intramolecular cyclization on alkali treatment of 38 that was responsible for the non-observation of the 3,4 cleavage would not be of importance in the case of 2-methyl 3-benzamido 4-quinazolone (56) because of the vastly reduced electrophilic character of the 3-substituent. 2-Methyl 3-benzamido 4-quin azolone (56)[9] was prepared by an improved procedure in 85% yield by reaction of 3-amino 2-methyl 4-quinazolone (55)[8] with benzoyl chloride/pyridine.

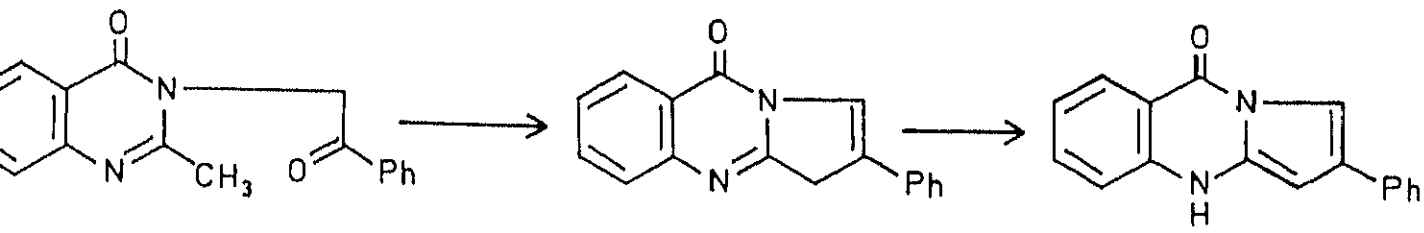
56: mp : 182°C (lit.[9] mp 182°C)

ir : ν_{max} (KBr) cm^{-1}; 3180 (-NH), 1700 (-CO), 1670 (-CO)

nmr : δ ($CDCl_3$), 60 MHz: 2.4 (s, 3H, $-C\underline{H}_3$), 7.0-8.2 (m, 9H, aromatic), 9.6 (s, 1H, exch. D_2O, N$\underline{H}$).

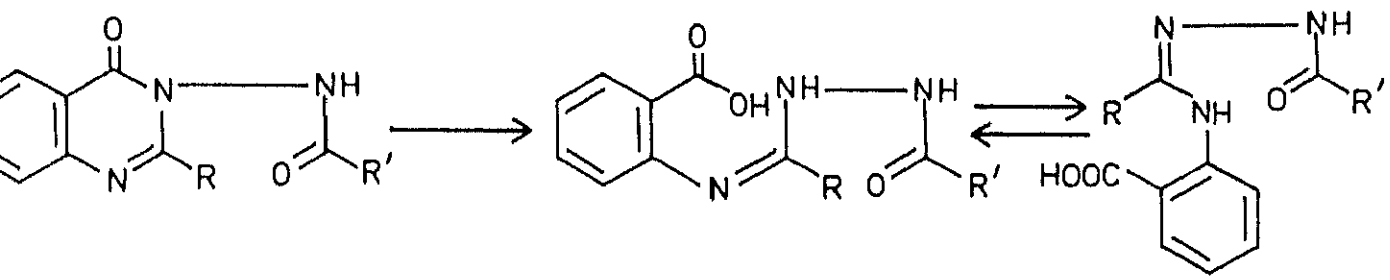
The reaction of 56 in refluxing 1N NaOH, gave an acid, mp 245-246°C, which afforded in quantitative yields, the corresponding methyl ester, mp 159-161°C. This compound has been assigned structure 58 on the basis of spectral and analytical data. The carboxylic acid mp 245-246°C therefore possesses structure 57. The isolation of the triazole carboxylic acid 57 in 35% yields is in contrast to the reported failure to isolate products on treatment of 56 with dilute alkali[10] (CHART II.C.6).

CHART II.C.5



38 53 54

CHART II.C.6

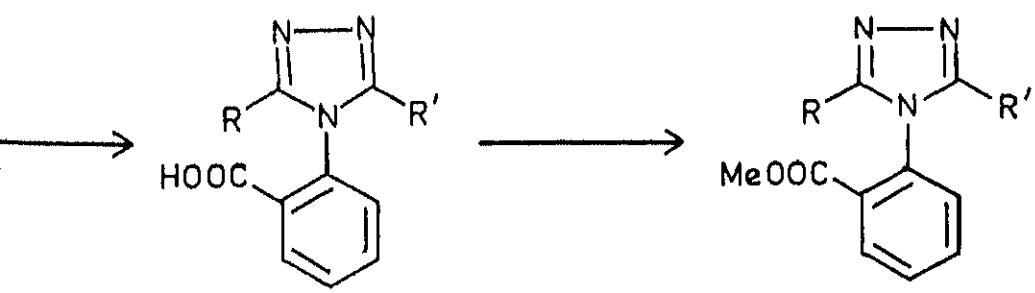


6: R = Me; R′ = Ph

1: R = R′ = Ph

4: R = Me; R′ = t_{Bu}

59 R = Me; R′ = Ph



57: R = Me; R′ = Ph

62: R = R′ = Ph

58: R = Me; R′ = Ph

63: R = R′ = Ph

---

57 : mp : 245-246°C

58 : mp : 159-161°C

ir : ν_{max} (KBr) cm^{-1}; 1720 (-CO)

nmr : δ($CDCl_3$),60 MHz : 2.3 (s, 3H, $-C\underline{H}_3$), 3.6 (s, 3H, $-COOC\underline{H}_3$), 7.2-8.2 (m, 9H, aromatic)

m/z : 293 (M^+), 234 (M^+ - COOMe)

The formation of compound 57 must involve the anticipated 3,4-bond cleavage - parallel to that of the ATP-Imidazole cycle (CHART I.C.1) - leading to the carboxylic acid intermediate 59. Either the isolation of 59 or its further transformation along the pathways of the Natural cycle and initiated by addition to the 1,2-bond, was not possible because of the pronounced tendency to form the triazole 57, promoted by processes involving the appropriate amidine nitrogen. It appears that the 2-substitution of the quinazolone not only prevented the unwanted acceptance of hydroxide at this position - which results in the 2,3-bond rupture - but also blocked the intramolecular cyclization at this site, a necessary step towards formation of the daughter products.

The realization that the desired 3,4-bond cleavage could be achieved by the incorporation of a 2-substituent,

made it attractive to isolate the product arising from the primary cleavage, since, it could be transformed to daughter products under a variety of conditions. It was hoped that this might be accomplished by incorporating a sufficiently bulky substituent that would also prevent the formation of triazoles.

With the above objective, 2-phenyl 3-benzamido 4-quinazolone (61)[12] was prepared by reaction of 3-amino 2-phenyl 4-quinazolone (60)[9] with benzoyl chloride/pyridine in 74% yields.

---

61 : mp : 200°C (lit.[11] mp 202°C)

ir : ν_{max}(KBr) cm^{-1}; 3160 (-NH), 1710 (-CO), 1670 (-CO)

A suspension of 61 in 1N NaOH was refluxed for 12 hours. The clear solution on cooling precipitated a sodium salt of an acid which on acidification yielded a carboxylic acid, mp. 319-320°C. This acid gave in quantitative yields the corresponding methyl ester whose structure has been established as the triazole 63, on the basis of spectral and analytical data. Consequently, the carboxylic acid has structure 62. The isolation of the acid 62 in 50% yields from 61 follows a

---

64 : mp : 164-166°C

ir : ν_{max}(KBr) cm^{-1}; 3300 (-NH), 1718 (-CO), 1675, 1615

nmr : δ($CDCl_3$), 60 MHz: 1.4 (s, 9H, ^{t}Bu), 2.4 (s, 3H, $-C\underline{H}_3$), 7.4-8.5 (m, 5H, aromatic).

However, the reaction of 64 with dilute alkali, under a variety of conditions, gave intractable glassy solids.

The reaction corresponding to the 3,4-bond cleavage of these models takes place in the Natural cycle (CHART I.C.1) in a purely hydrolytic manner. Consequently, it was felt that the action of water alone on models such as 61 could provide alternate, hopefully desirable pathways. In the event, the reaction of 61 with distilled water in a sealed tube at 200°C gave, on careful chromatography, 3,4,5-triphenyl 1,2,4-triazole (65, 8%)[12], 2-phenyl 4-quinazolone (66, 8%)[13], benzamide (67, 19%), benzhydrazide (68, 15%) and benzanilide (69, 41%).

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65 : mp : 296-297°C (lit.[12] mp 299°C)

m/z : 297 (M^+)

66 : mp : 229°C (lit.[13] mp 223°C)

67 : mp : 126-128°C (lit. mp 128-129°C)

m/z : 122 $(M+1)^+$

68 : mp : 110-112°C (lit. mp 112°C)

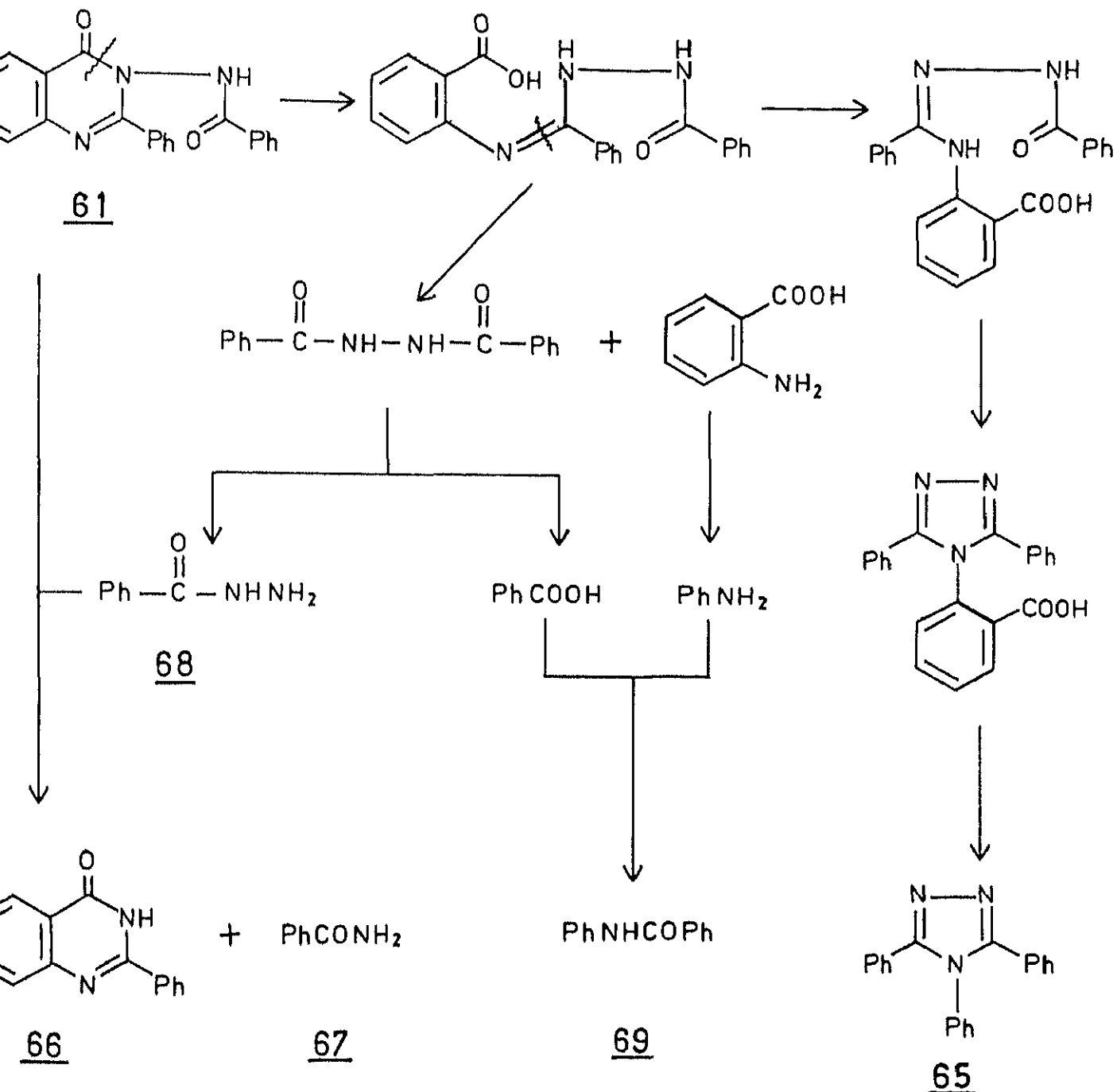
m/z : 136 (M^+)

69 : mp : 163-164°C (lit. mp 162-164°C)

m/z : 197 (M^+).

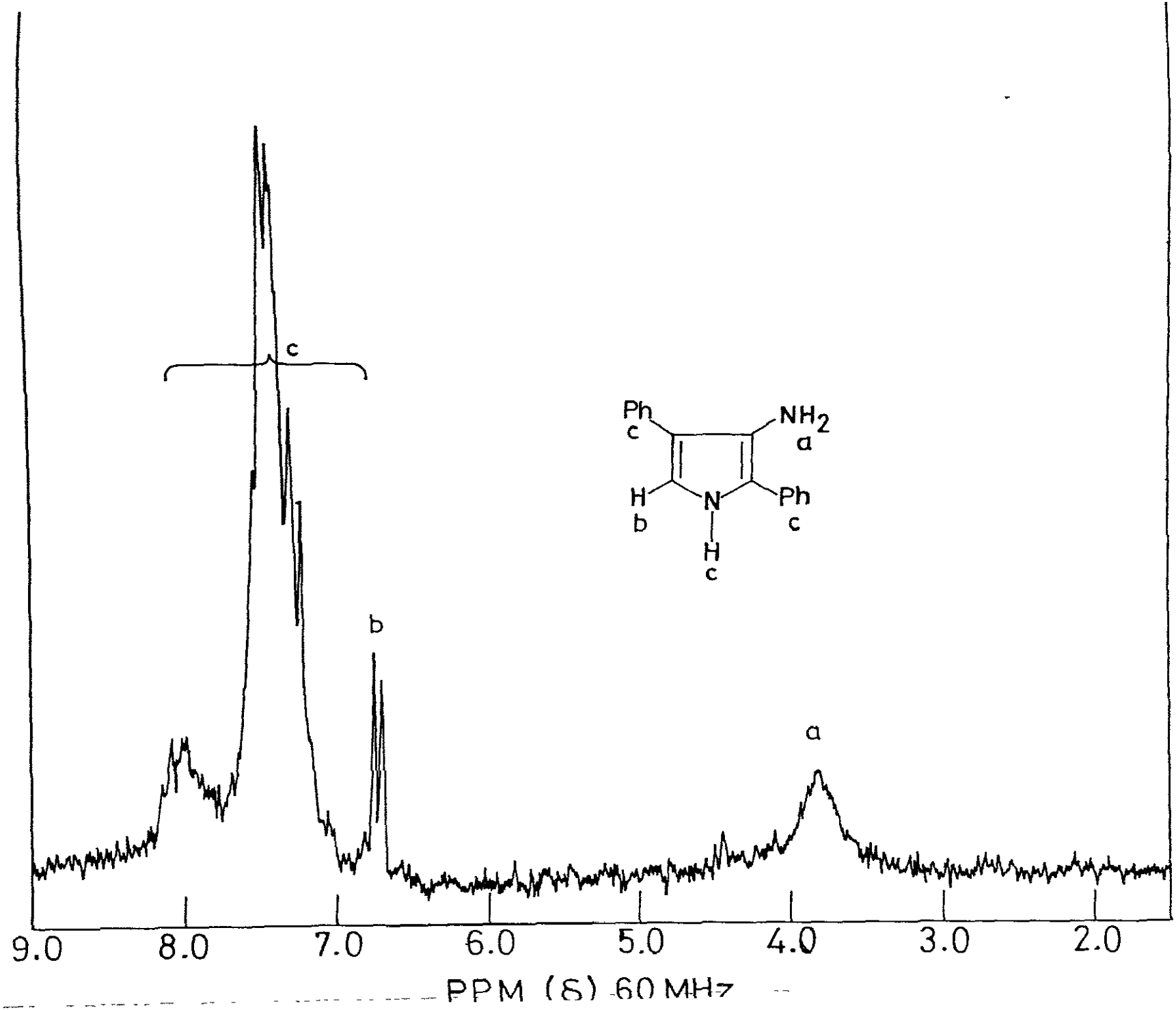
The rationalization of the multitude of products from 61 with water are given in CHART II.C.7. The genesis of all the observed products can be best understood on the basis of the expected 3,4-bond cleavage. The open carboxylic acid intermediate thus formed could undergo either cyclization leading to triazole 65, or complete hydrolysis giving rise to anthranilic acid and dibenzhydrazide. The latter on hydrolysis could lead to benzoic acid and benzhydrazide, which, being a recognized di-imide precursor, could reduce 61 to 2-phenyl 4-quinazolone (66) and benzamide (67). Systems similar to 61 are known to undergo reduction leading to 4-quinazolone[14] (4). The formation of benzanilide could be explained on the basis of the reaction of benzoic acid with aniline, arising from decarboxylation of anthranilic acid. Thus, it appears that this interesting hydrolytic experiment led to practically every possible mode of cleavage, an important exception being the formation of the anticipated derived product, namely, 2,5-diphenyl oxadiazole. Parenthetically, blank experiments have established that dibenzhydrazide does not form the

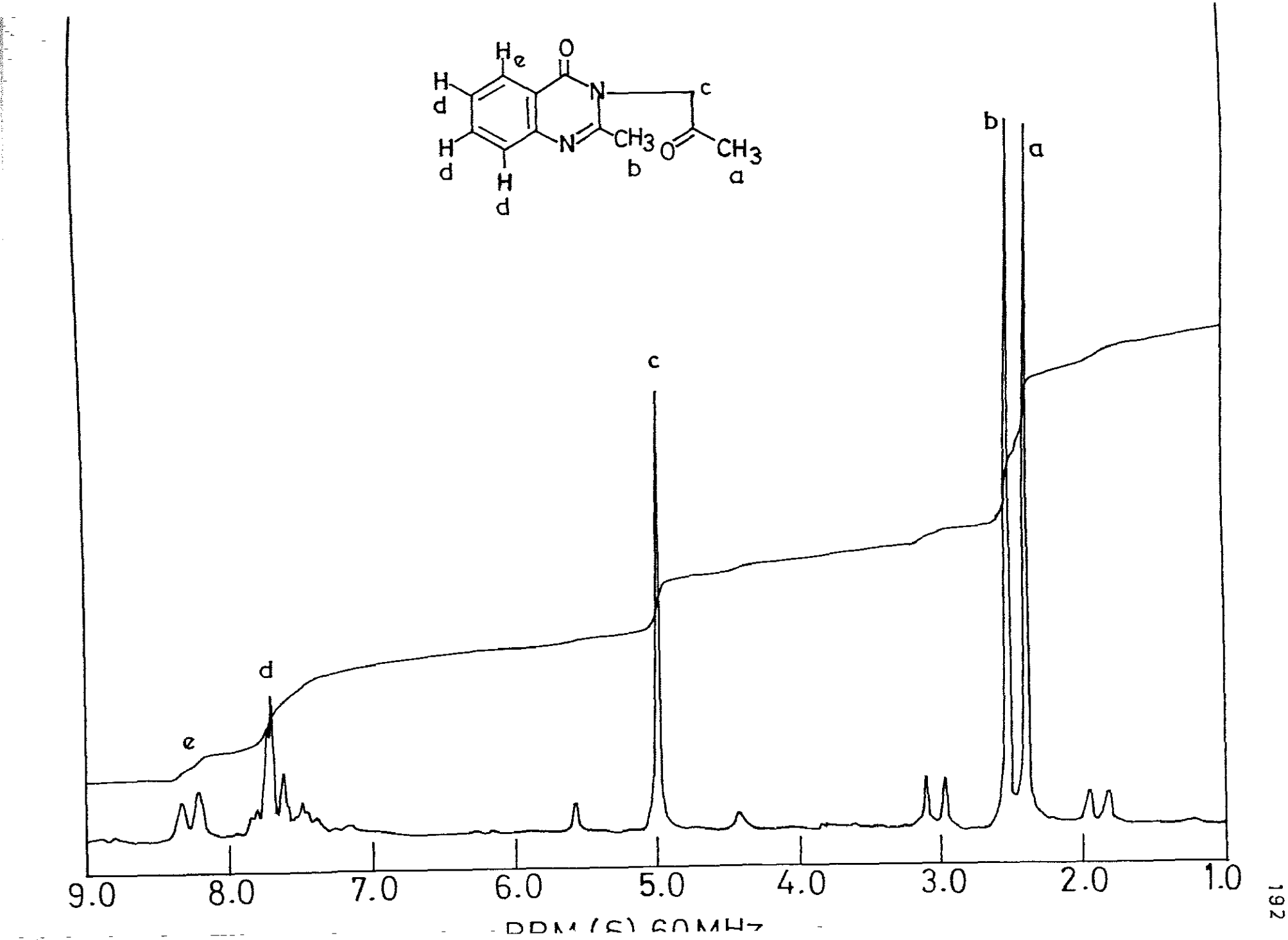
CHART II.C.7

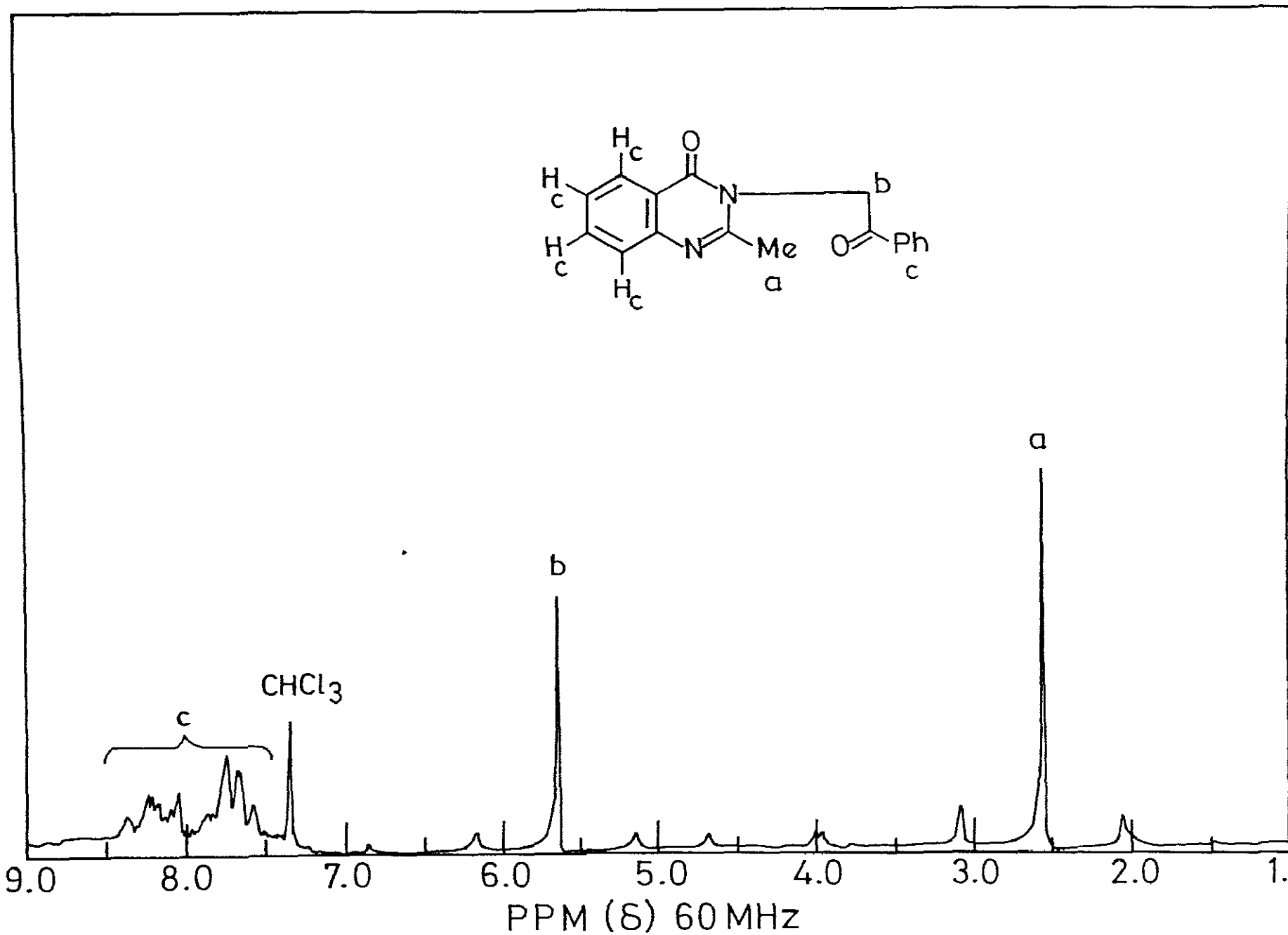


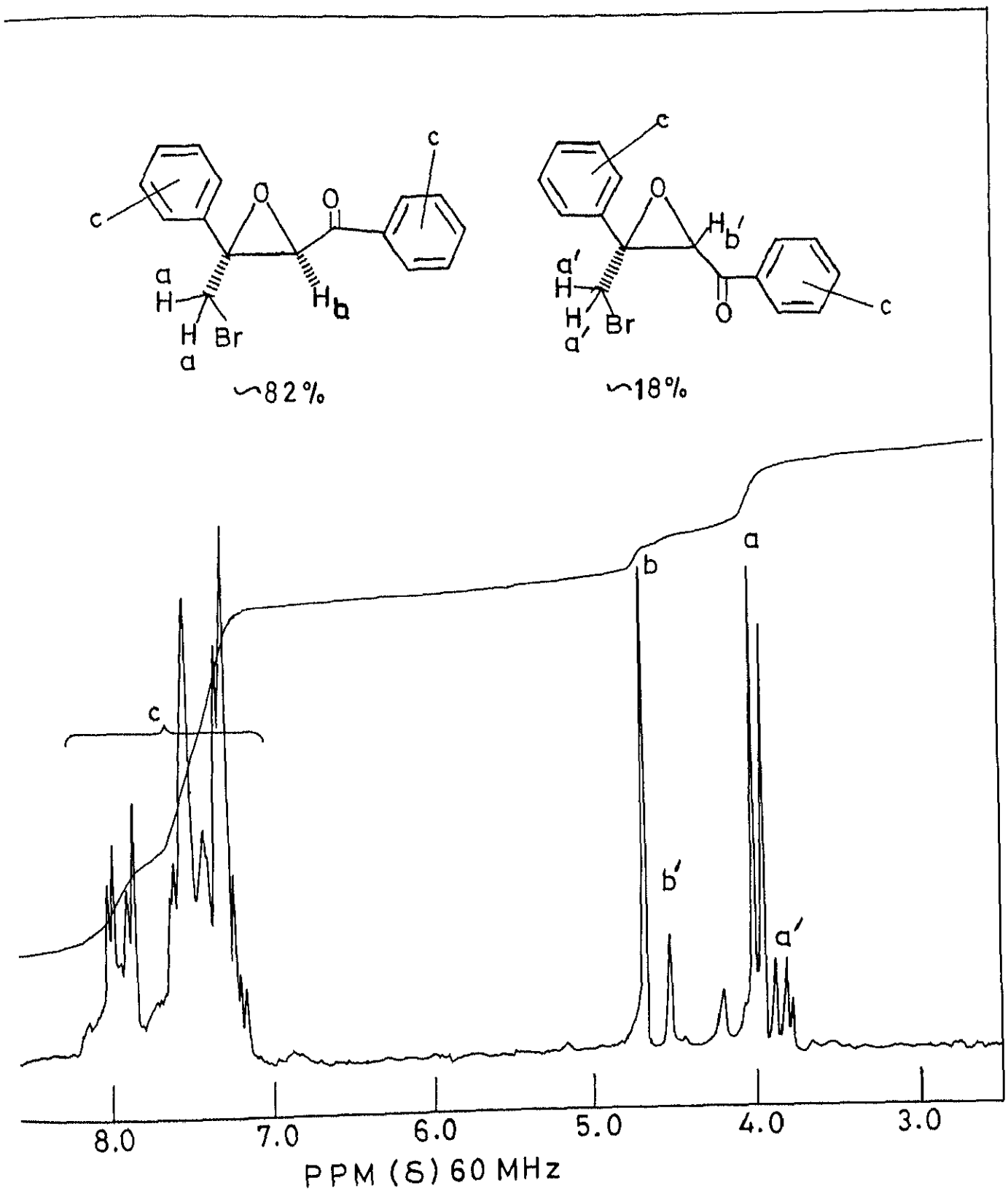
oxadiazole under the conditions of the hydrolytic cleavage and consequently it must, if at all, arise from the open chain carboxylic acid intermediate.

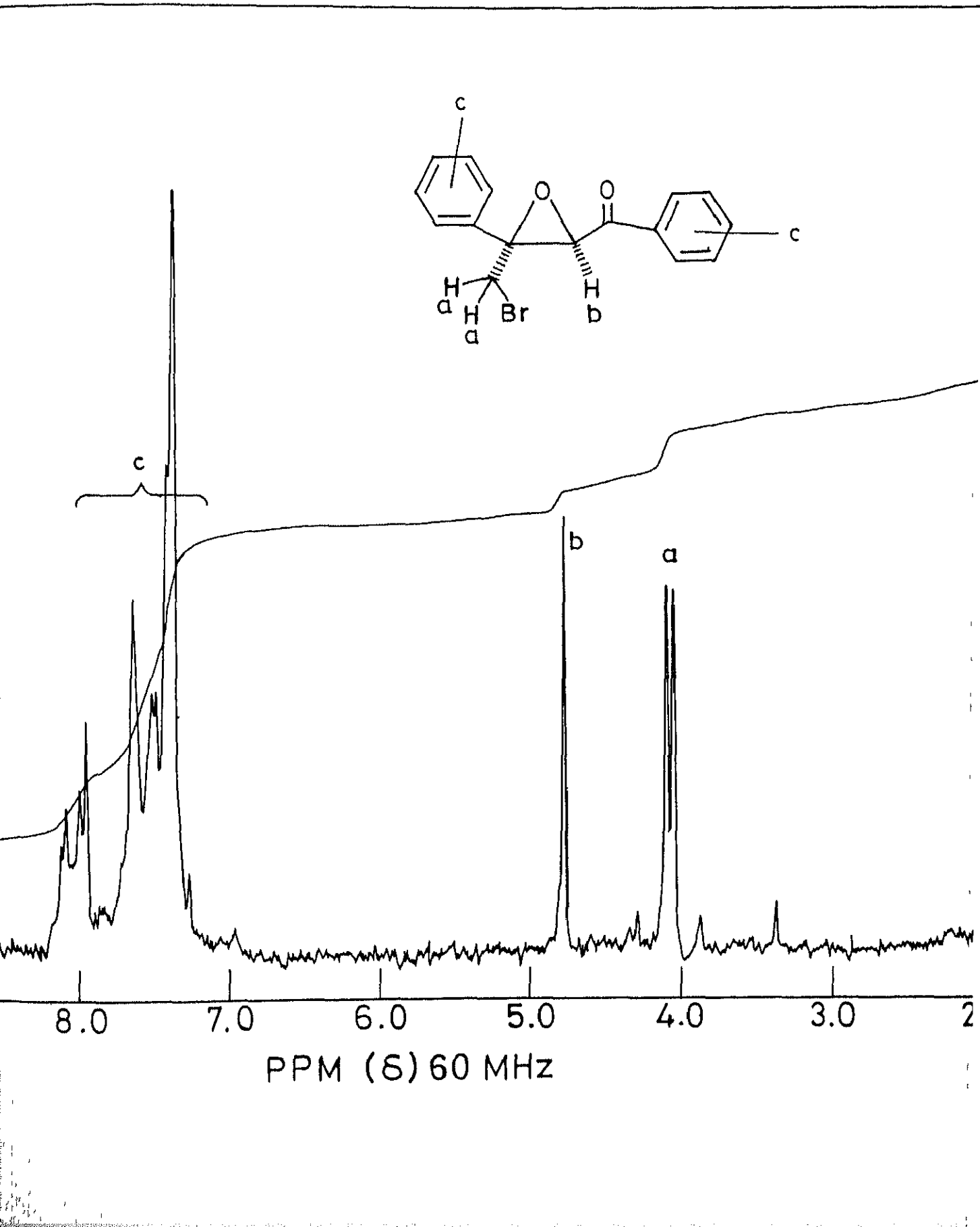
The spectrum of experiments described above, could have led to the demonstration of the generation of oxygen heterocycles on anthranilic acid template. The infructuous outcome must be attributed to the deficiencies in planning rather than to the proposition that it may not be possible to extrapolate the template synthesis of imidazole - along the lines of the ATP-Imidazole cycle - to other heterocycles. Further work would, hopefully, provide a satisfactory solution eventually.

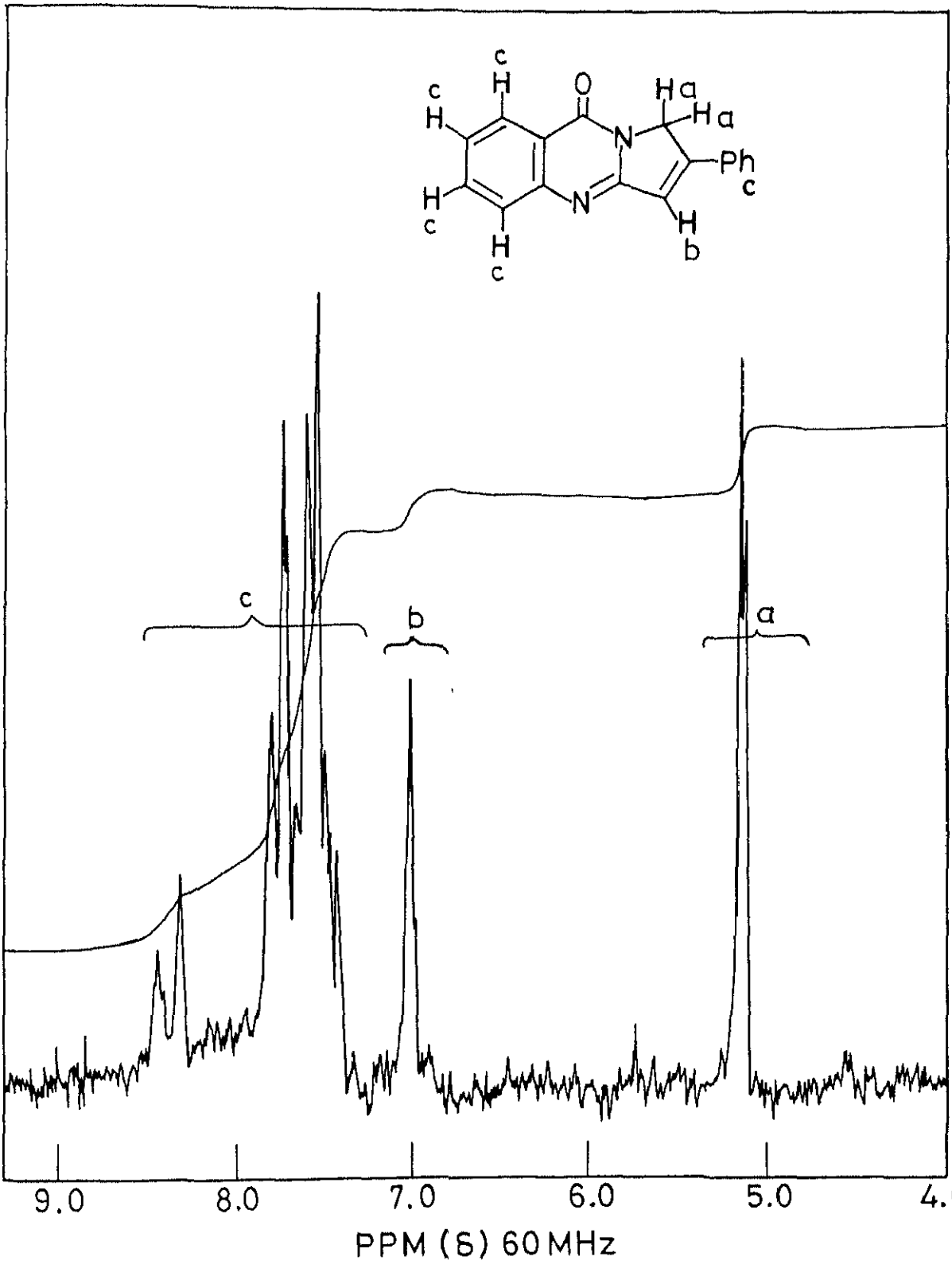

c
b
a
Ph
c
NH2
a
H
b
N
Ph
c
H
c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 MHz

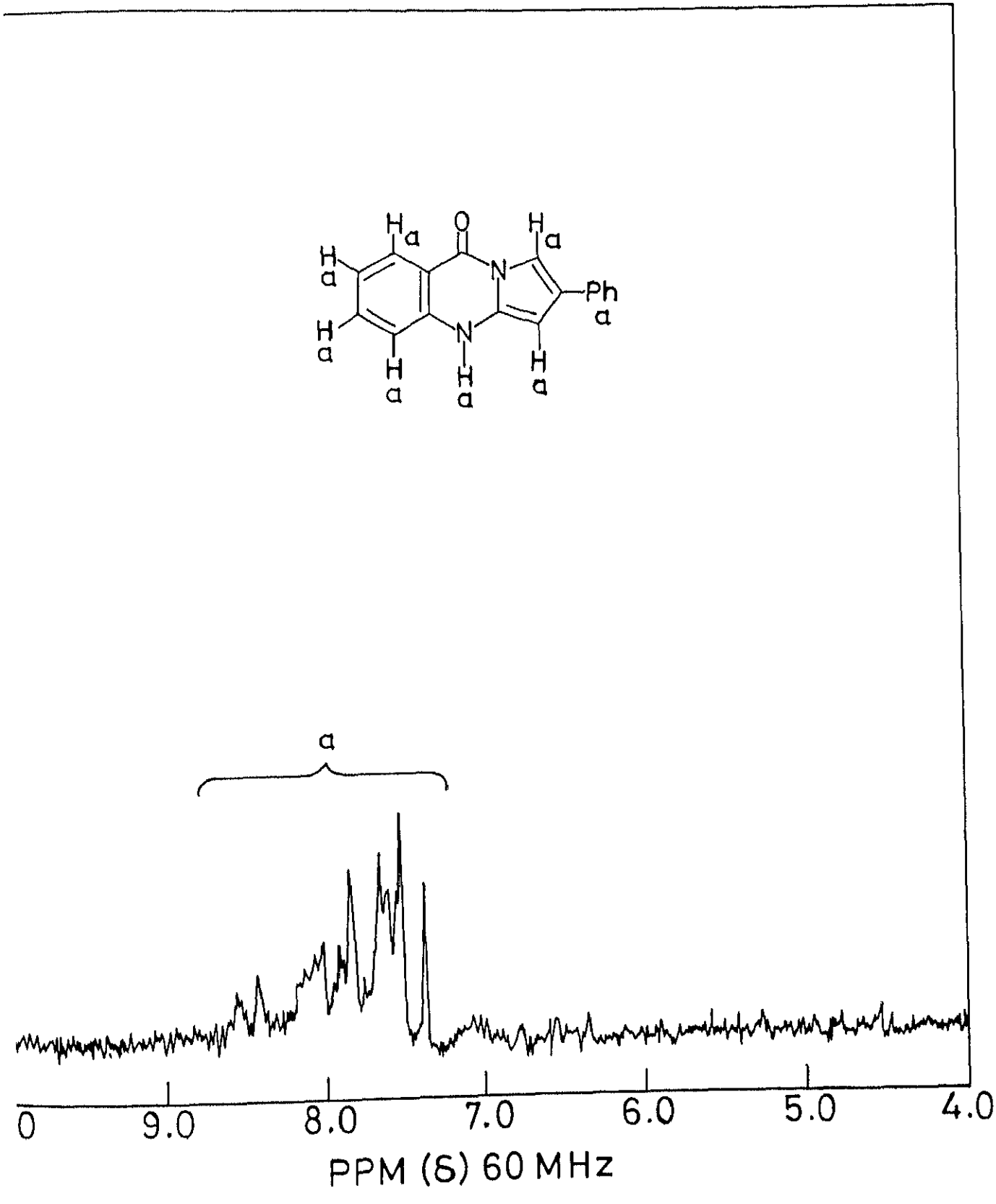

He
O
H
d
H
d
H
d
N
N
CH3
b
c
O
CH3
a
b
a
c
d
e
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60MHz

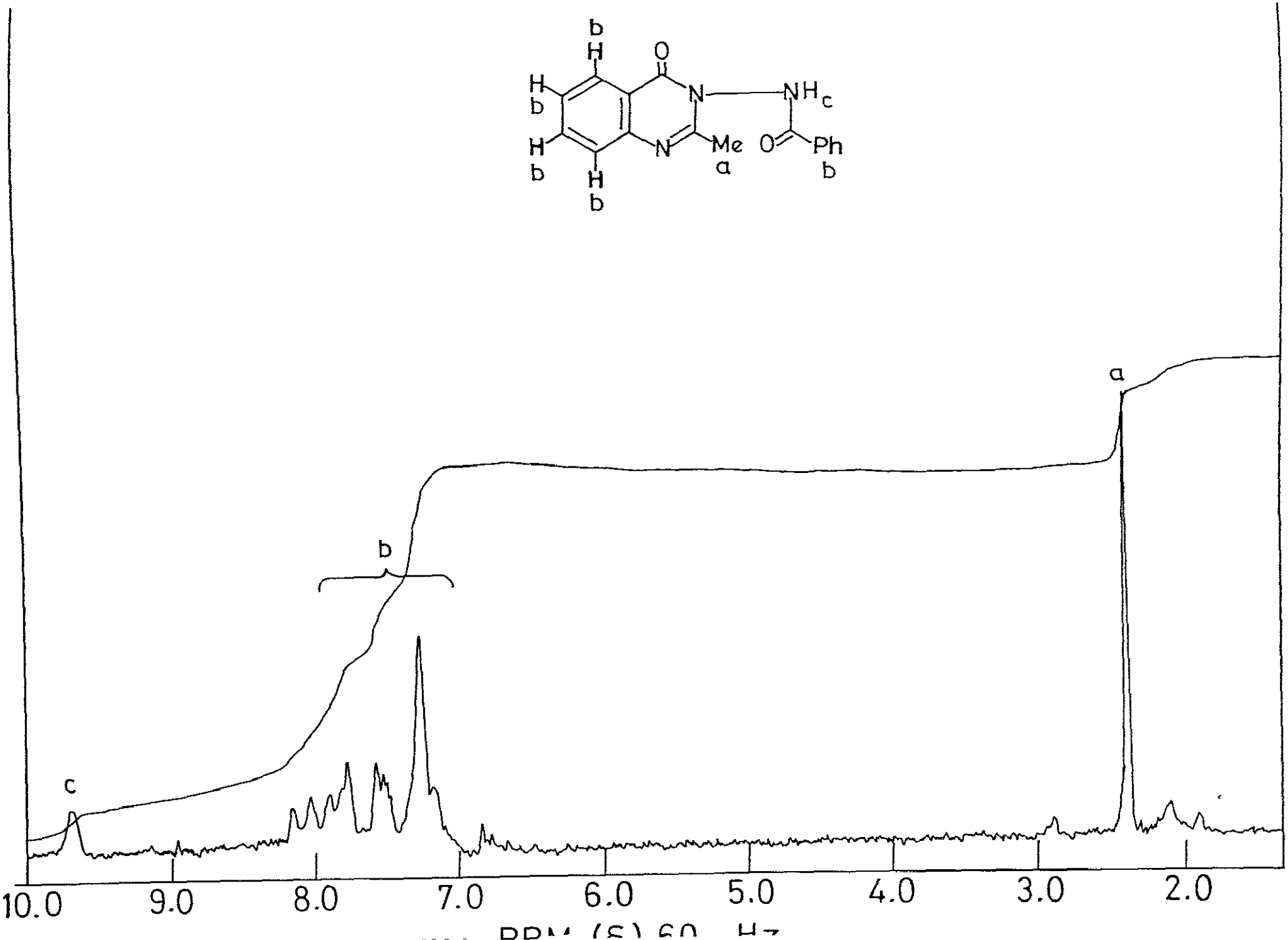

H
c
O
N
b
H
c
Me
a
O
Ph
c
H
c
H
c
a
b
CHCl3
c
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM (δ) 60 MHz

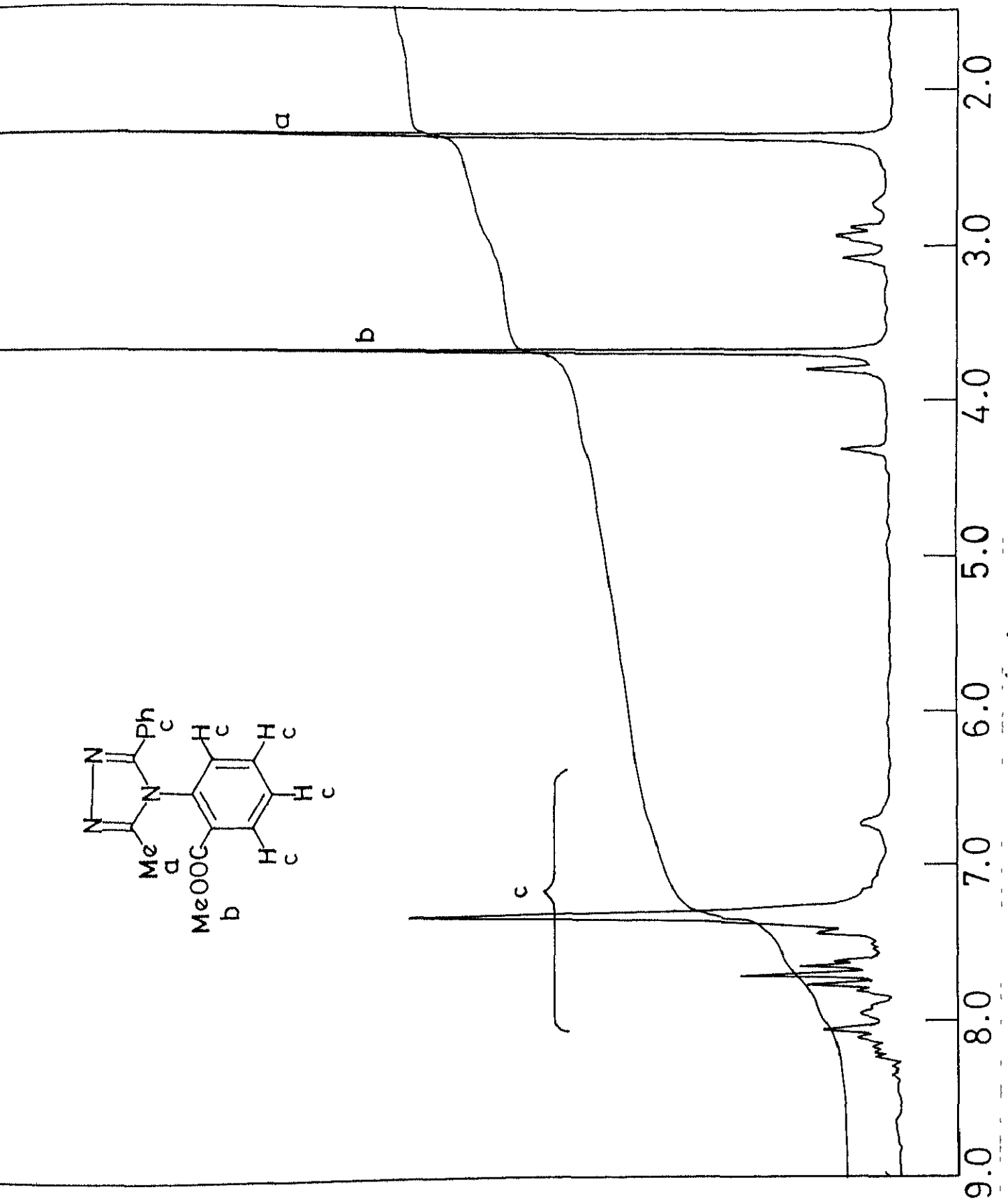

c
O
O
c
a
H
H
Br
a
H_b
~82%
c
O
$H_{b'}$
a'
H
H'
Br
a'
O
c
~18%
c
b
a
b'
a'
8.0
7.0
6.0
5.0
4.0
3.0
PPM (δ) 60 MHz

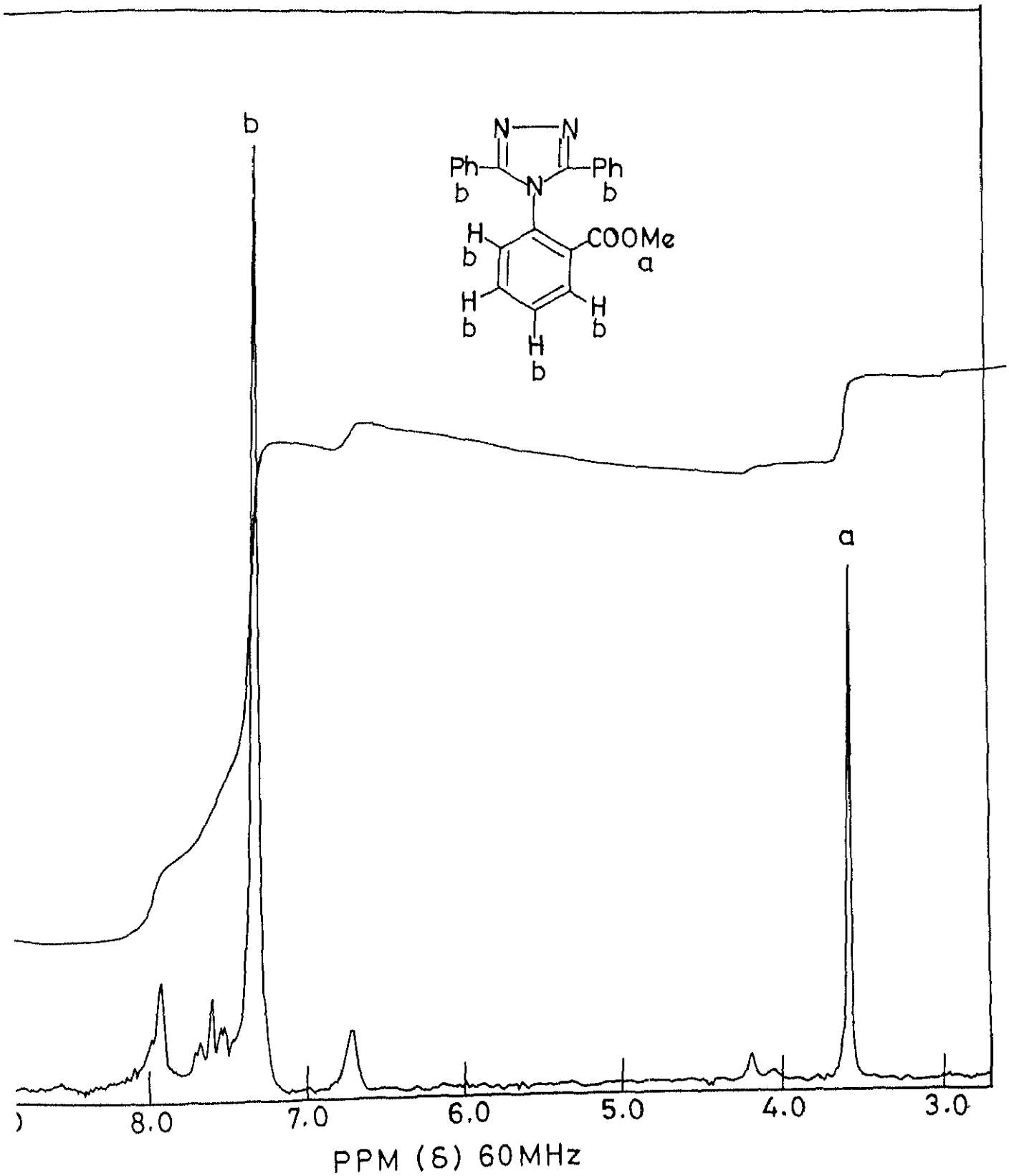

c
O
O
c
H
a
H
a
Br
H
b
c
b
a
8.0
7.0
6.0
5.0
4.0
3.0
2
PPM (δ) 60 MHz

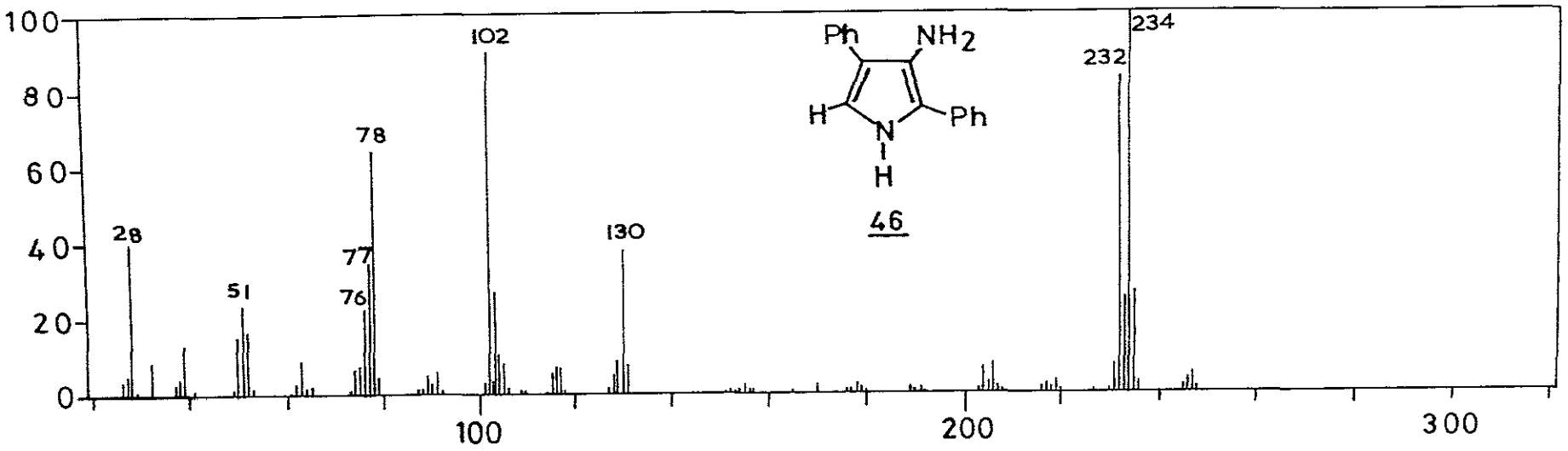

c
H
c
H
O
Ha
Ha
N
Ph
c
H
c
N
H
b
H
c
c
b
a
9.0
8.0
7.0
6.0
5.0
4.0
PPM (δ) 60 MHz

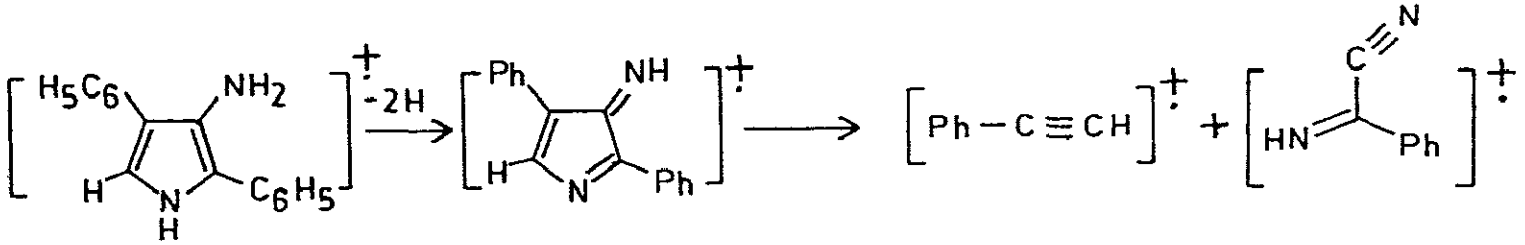

Ha
O
Ha
Ha
N
Ph
a
Ha
N
Ha
Ha
Ha
a
0
9.0
8.0
7.0
6.0
5.0
4.0
PPM (δ) 60 MHz


b
H
O
H
b
N
NH
c
H
b
N
Me
a
O
Ph
b
H
b
b
a
c
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
PPM (δ) 60 Hz

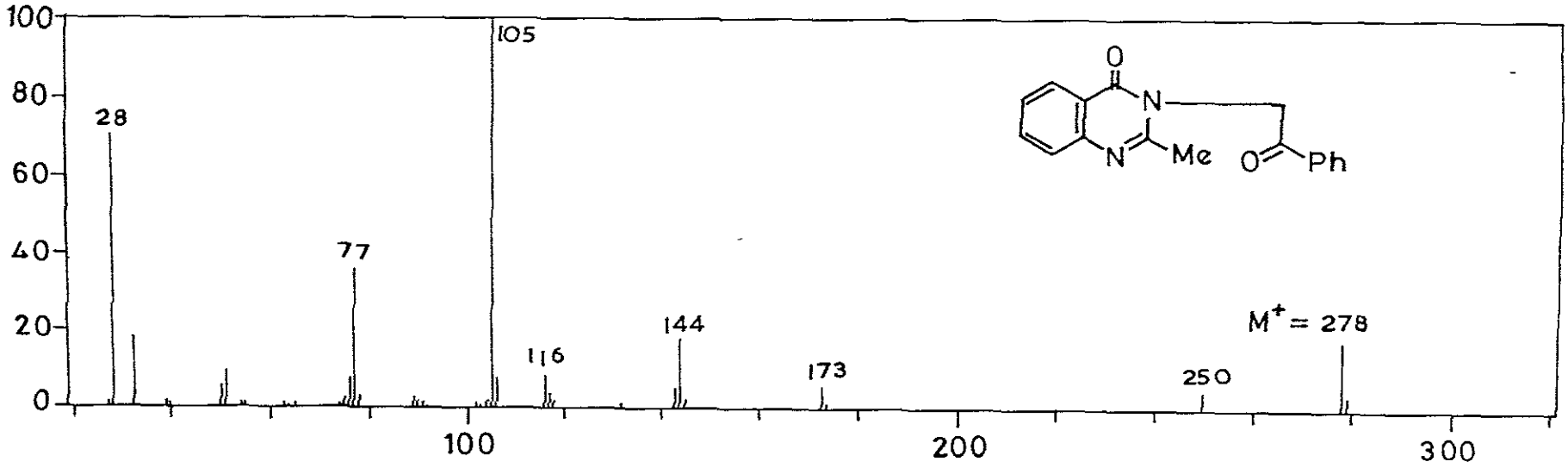

a
b
c
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
Ph
c
H
c
H
c
H
c
H
c
N
N
N
Me
a
MeOOC
b

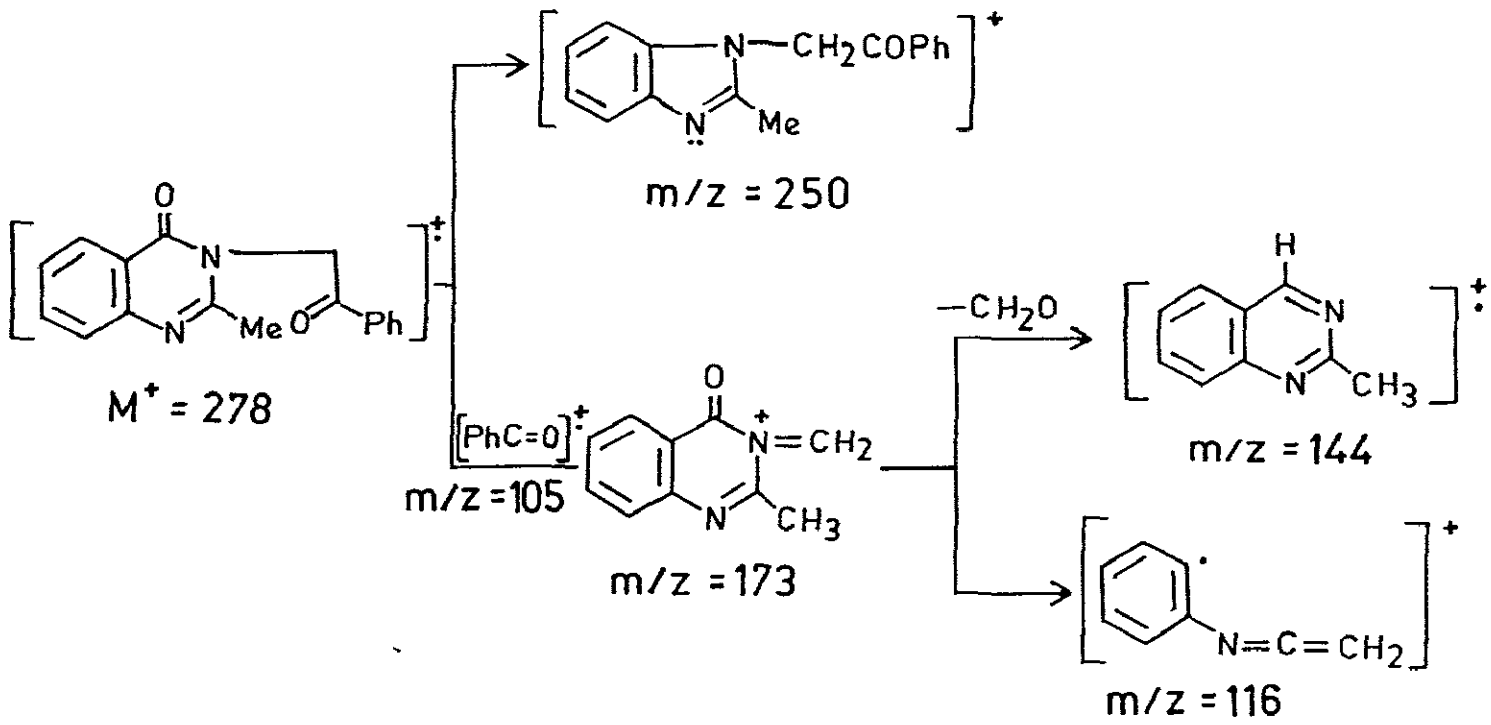

b
N
N
Ph
b
Ph
b
N
H
b
COOMe
a
H
b
H
b
H
b
b
a
8.0
7.0
6.0
5.0
4.0
3.0
PPM (δ) 60MHz

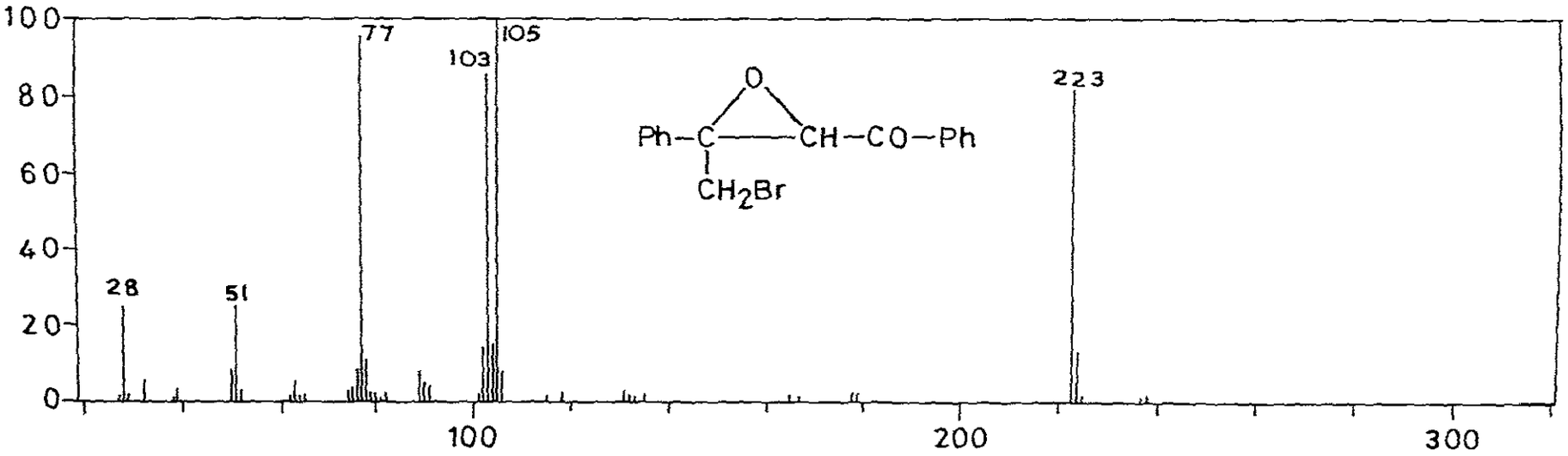


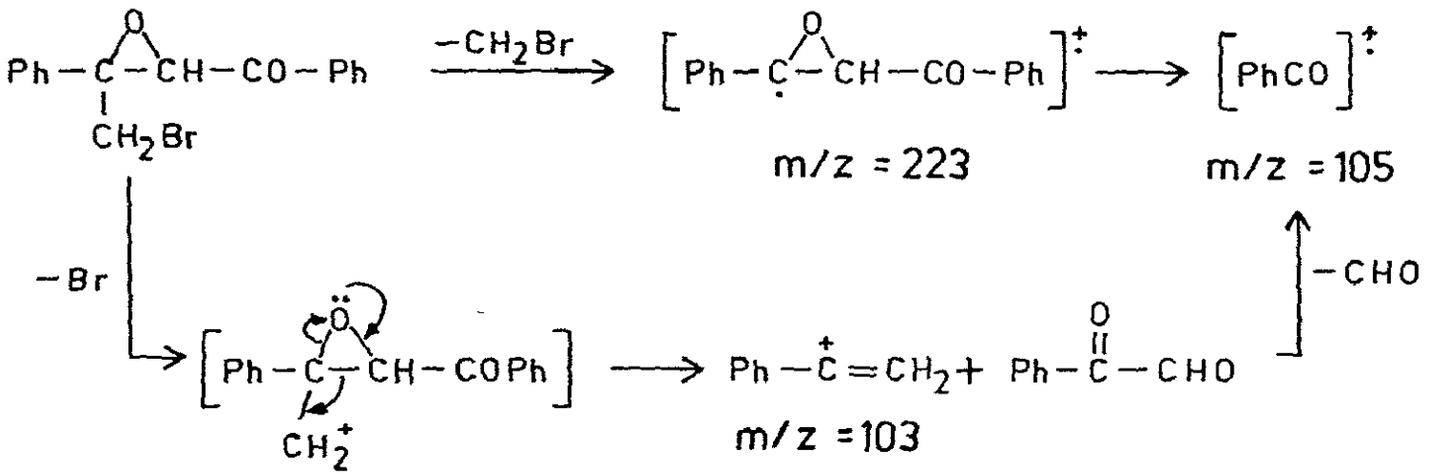


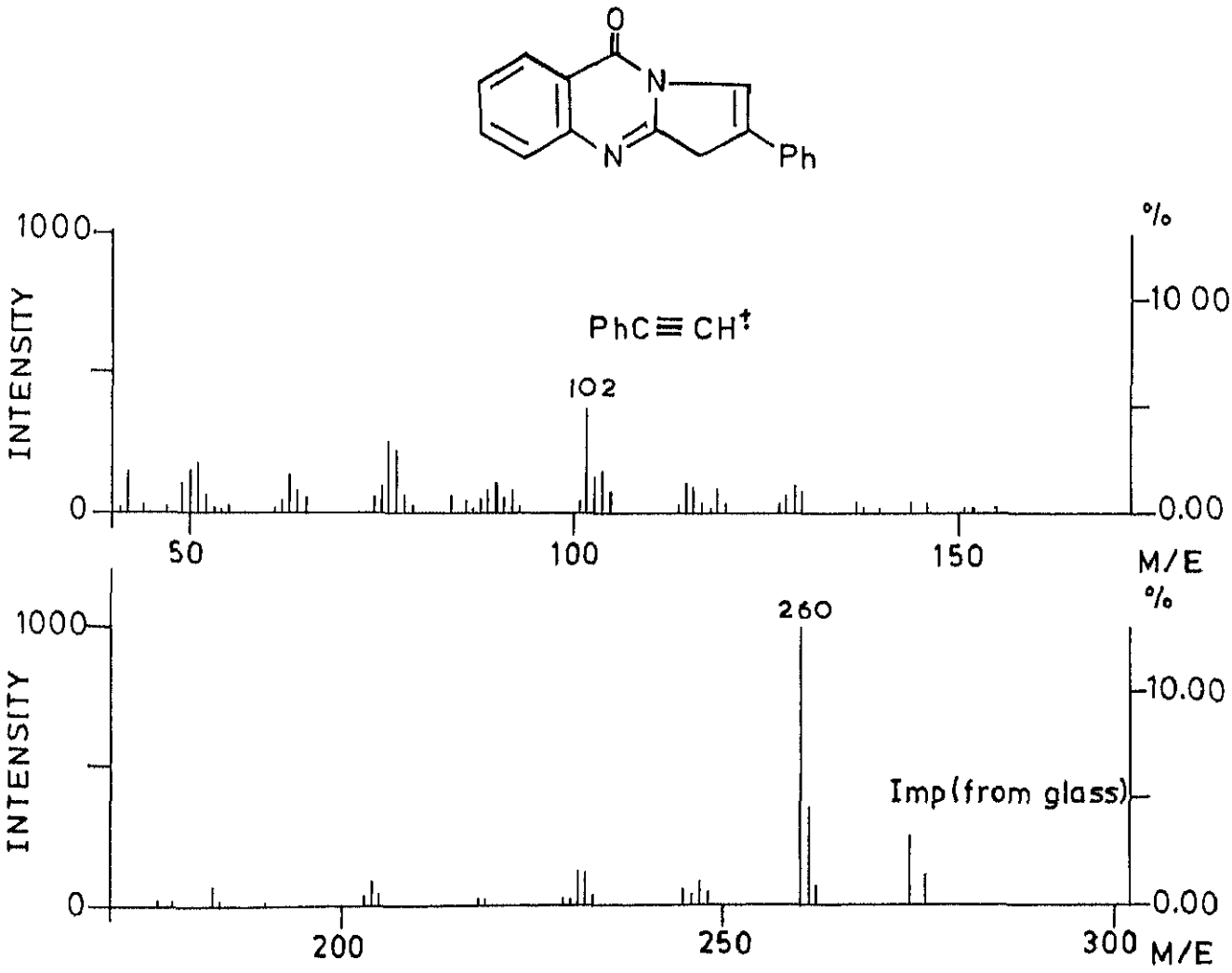
$M^+ = 234$ m/z = 232 m/z = 102 m/z = 130

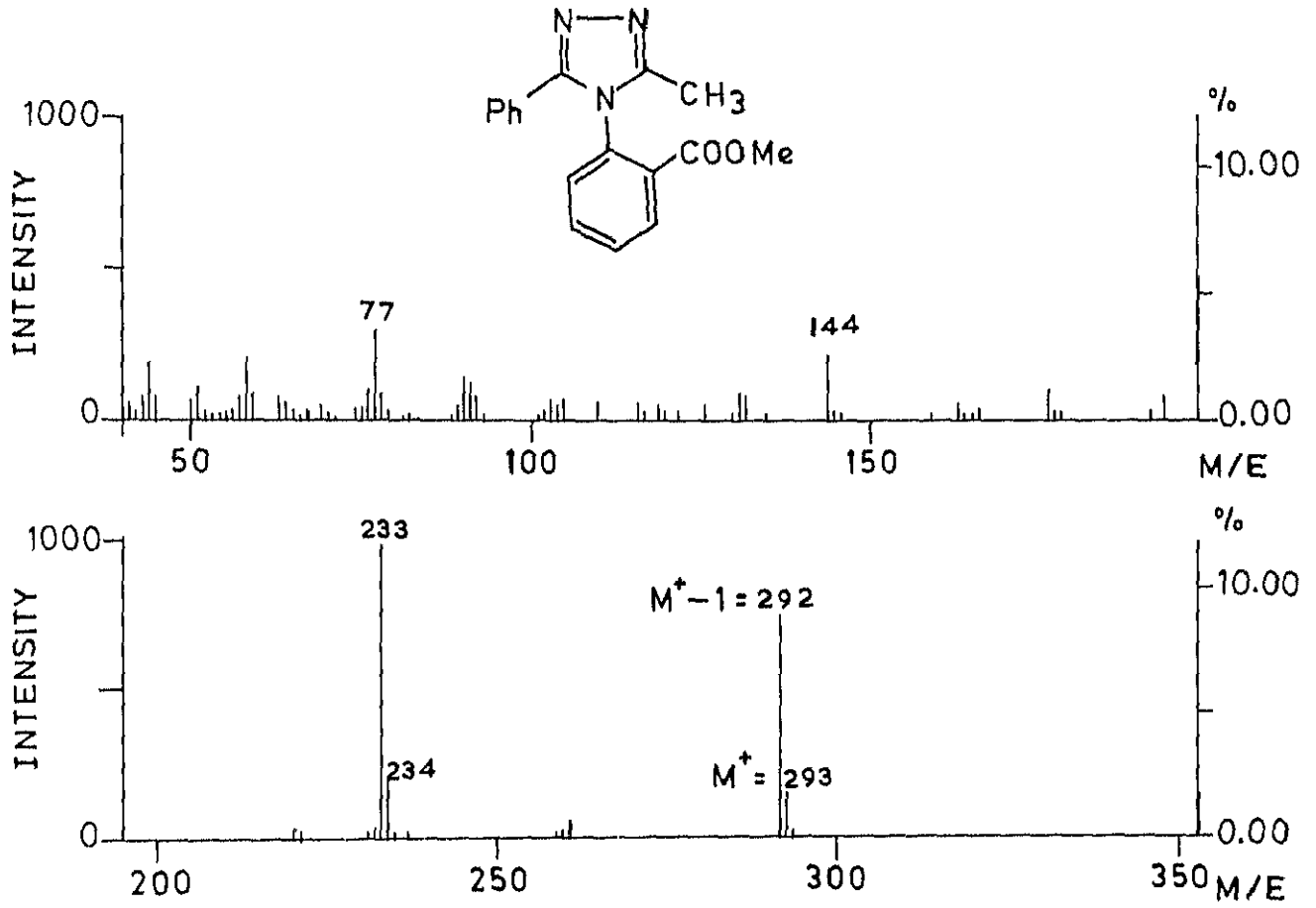

100
80
60
40
20
0
28
77
105
116
144
173
250
M+ = 278
100
200
300
O
N
Me
O
Ph

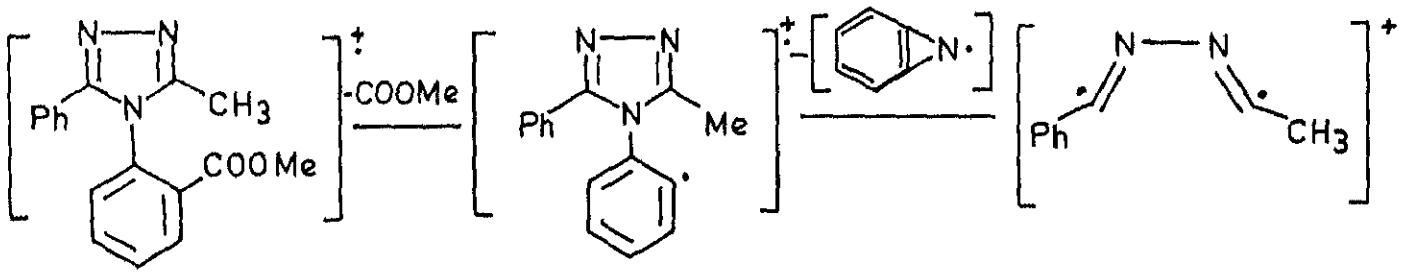

N—CH2COPh
N
Me
m/z = 250
O
N
Me
O
Ph
M+ = 278
[PhC=O]+
m/z = 105
O
N+=CH2
N
CH3
m/z = 173
−CH2O
H
N
N
CH3
m/z = 144
N=C=CH2
m/z = 116


100
80
60
40
20
0
77
105
103
223
28
51
100
200
300
O
Ph–C
CH–CO–Ph
CH2Br


Ph–C–CH–CO–Ph
CH2Br
–CH2Br
[Ph–C–CH–CO–Ph]+
[PhCO]+
m/z = 223
m/z = 105
–Br
–CHO
[Ph–C–CH–COPh]
CH2+
Ph–C=CH2 +
Ph–C–CHO
m/z = 103


O
N
N
Ph
1000
INTENSITY
0
PhC≡CH⁺
102
%
10 00
0.00
50
100
150
M/E
1000
INTENSITY
0
260
Imp(from glass)
%
10.00
0.00
200
250
300
M/E





$M^+ = 293$
$(M^+-1) = 292$

m/z = 234

m/z = 144

II.E. EXPERIMENTAL[15]

I. The reaction of 3-phenacyl 4-quinazolone (6) with aqueous alkali: Isolation of 3-amino 2,4-diphenyl pyrrole (46) and anthranilic acid (45):

A suspension of 6 (0.310 g, 1.17 mmol) in aqueous NaOH (0.6 N, 30 ml) was refluxed for 16 hours, cooled, extracted with ethyl acetate (3 x 25 ml), dried, evaporated, and the residue on crystallization from ethanol gave greenish yellow needles, 0.103 g (37%) of 46, mp 180-181°C (lit.[2] mp 178-179°C).

tlc : PhH:EtOAc ::80:20; Rf. 0.7

ir : ν_{max}(KBr) cm^{-1}, 3430, 3240 ($-NH_2$), 1615 (C=N)

nmr : $\delta(CDCl_3)$, 60 MHz : 3.67 (br, 2H, exch. D_2O-$N\underline{H}_2$), 6.6 (d, J = 3Hz, 1H, 5-pyrrole proton), 6.87-8.1 (m, 11H, -N$\underline{H}$ and aromatic)

m/z : 234 (M^+).

The aqueous layer was adjusted to pH ~7 with 2N H_2SO_4, extracted with CH_2Cl_2 (3x20 ml), dried, evaporated and the residue on crystallization from benzene gave 0.073 g (45%) of 45, mp 144°C (lit. mp 144-146°C).

II. 2-Methyl 4-quinazolone (36)

Acetanthranil:

A mixture of anthranilic acid (45) (28 g, 204 mmol) and Ac_2O (100 ml) was refluxed for 2 hours, solvents evaporated in vacuo and the residue on crystallization from CCl_4/hexane gave 24 g (72%) of acetanthranil, mp 79°C (lit.[4] mp 82°C).

2-Methyl 4-quinazolone (36):

A mixture of acetanthranil (32 g, 200 mmol) and NH_4OAc (35 g, 450 mmol) was held at 170-180°C for 0.2 hour, cooled and crystallized from hot water to yield 14 g (43%) of 36, mp 230°C (lit.[4] mp 233°C).

tlc : PhH:EtOAc::20:80; Rf. 0.3

ir : ν_{max}(KBr) cm^{-1}; 3400, 2860 (-NH), 1670 (-CO)

III. The reaction of 2-methyl 4-quinazolone (36) with phenacyl bromide: Preparation of 2-methyl 3-phenacyl 4-quinazolone (38) and isolation of phenacyl bromide condensation products 52a + 52b

Phenacyl bromide (12.13 g, 61 mmol) was added to a solution of the potassium salt of 2-methyl 4-quinazolone (36) - prepared from 36 (10.66 g, 66.6 mmol) and 1M KOH in dry ethanol (95 ml) - left stirred at rt. overnight, the filterate evaporated and the residue chromatographed on silica gel.

Elution with PhH:EtOAc :: 90 :10 gave a compound, mp 135°C which was subsequently identified as mixture of 52a + 52b, yield 2g (21%).

tlc : PhH. EtOAc ::50 :50; Rf. 0.8

ir : ν_{max}(KBr) cm^{-1}; 1665 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz: 52a + 52b :: 1 :4, 3.8(dd, 52a), 3.9 (d, 52b), 4.4 (s, 52a), 4.6 (s, 52b), 7.4 (m, ar).

Further elution with PhH:EtOAc :: 70 :30 gave 4.5 g (24%) of 38, mp 164°C

tlc : PhH:EtOAc ::50 :50; Rf. 0.4

Anal. Cald. for $C_{17}H_{14}N_2O_2$ (Mol. Wt. 278)
C, 73.3; H, 5.0; N, 10.0%

Found : C, 73.1; H, 4.7, N, 9.97%

ir : ν_{max}(KBr) cm^{-1}; 1670 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz : 2.46 (s, 3H, $-C\underline{H}_3$), 5.39 (s, 2H, $-C\underline{H}_2COPh$), 7.26-8.36 (m, 9H, aromatic)

m/z : 278 (M^+).

IV. The reaction of phenacyl bromide with methanolic KOH: Isolation of 52a + 52b

A solution of phenacyl bromide (0.154 g, 0.8 mmol) in 0.25 M KOH (3 ml) was left stirred at rt. for 2 days, filtered and evaporated. Preparative tlc using benzene gave 0.078

(32%) of 52a + 52b, mp 135-136°C.

V. Isomerization of 52a + 52b → 52b

A solution of 52a + 52b (0.100 g, 0.3 mmol), mp 135-136°C) in 0.06 M KOH (5 ml) was refluxed for 0.5 hours and evaporated. Preparative tlc using benzene as developer gave 0.044 g (44%) of 52b, mp 162°C.

tlc : PhH:EtOAc:.50 50; Rf. 0.8

nmr : $\delta(CDCl_3)$, 60 MHz: 3.9 (d, 2H, $C\underline{H}_2Br$), 4.6 (s, 1H, $C\underline{H}$-COPh), 7.3-8.2 (m,10H, aromatic).

VI. The reaction of 2-methyl 3-phenacyl 4-quinazolone with aqueous alkali: Isolation of the tricyclic compound 53

A suspension of 38 (0.826 g, 2.97 mmol) in 7.5 N NaOH (40 ml) was refluxed for 14 hours, cooled, acidified with 2N H_2SO_4 (pH ~ 3), extracted with CH_2Cl_2 (3x20 ml), dried and evaporated to give 0.746 g (97%) of 53, mp 205-206°C

tlc : PhH:EtOAc::70:30; Rf. 0.6

ir : ν_{max} (KBr) cm^{-1}; 1665 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz; 5.05 (d, J = 0.5 Hz, 2H, allylic coupling), 6.9 (t, J = 0.5 Hz, 1H), 7.3-8.4 (m, 9H)

m/z : 260 (M^+).

VII. The thermal aromatization of 53 Isolation of the aromatic tricyclic system 54 :

Crystallization of 53, either from hot CH_2Cl_2 or from hot benzene led to quantitative isomerization to the aromatic compound 54, mp 185°C.

tlc : PhH:EtOAc::70 30; Rf. 0.6

ir : ν_{max} (KBr) cm^{-1}; 3400 (br, -NH), 1660 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz: 7.26-8.44 (m, aromatic)

m/z : 260 (M^+).

VIII. 2-Methyl 3-amino 4-quinazolone (55)

A mixture of acetanthranil, (5 g, 31 mmol) from (Experiment II) and 85% hydrazine hydrate (4 ml) was refluxed for 0.1 hour , the clear solution cooled, filtered, washed with benzene and dried to yield, 2g (37%) of 55, mp 147-148°C (lit.[8] mp 148°C).

IX. The reaction of 2-methyl 3-benzamido 4-quinazolone (56) with aqueous alkali : Isolation of 1-(o-carboxyphenyl)-3-phenyl 5-methyl triazole 57

2-Methyl 3-benzamido 4-quinazolone (56):

This compound was prepared by an improved procedure. A mixture of 2-methyl 3-amino 4-quinazolone (7 g, 0.04 mmol), benzoyl chloride (5.5 ml, 0.047 mol) and pyridine (10 ml,

0.123 mol) was stirred at rt. overnight, poured onto cold water (~ 200 ml), extracted with CH_2Cl_2 (2 x 100 ml), washed with water, dried and evaporated. The residue on crystallization from benzene-hexane gave 9g (85%) of 56, mp 182°C (lit.[9] mp 182°C).

tlc : PhH:EtOAc :70:30, Rf. 0.5

ir : ν_{max}(KBr) cm^{-1}, 3180 (-NH), 1700 (-CO), 1670 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz: 2.4 (s, 3H, $-CH_3$), 7 0-8.2 (m, 9H, aromatic), 9.6 (s, 1H, exch. D_2O, NH).

Hydrolysis of 56:

A suspension of 56 (3.5 g, 0.013 mol) in 1N NaOH (50 ml) was refluxed for 12 hours, cooled, extracted with ethyl acetate (5 x 50 ml) to remove 0.6g of unchanged 56, the aqueous layer acidified with 2N H_2SO_4, filtered, dried and crystallized from hot MeOH to give 1.2g (34%) of 57, mp 245-246°C.

X. The reaction of 57 with diazomethene: Preparation of triazole methyl ester 58

A methanolic solution of 57 was transformed with diazomethane in quantitative yields to 58, mp 159-161°C.

ir : ν_{max}(KBr) cm^{-1}: 1720 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz: 2.3 (s, 3H, $-CH_3$), 3.6 (s, 3H, $-COOCH_3$), 7.2-8.2 (m, 9H, aromatic)

m/z : 293 (M^+), 234 (M^+ -COOMe)

XI. 2-Phenyl 3-amino 4-quinazolone (60)

Benzanthranil:

A mixture of anthranilic acid (45) (2.74 g, 20 mmol), pyridine (50 ml) and benzoyl chloride (5.6 g, 40 mmol) was stirred at rt. overnight, poured onto water (~ 250 ml), filtered and the residue on crystallization from hot water gave 3.2 g (72%) of benzanthranil, mp 123°C (lit. 123°C).

2-Phenyl 3-amino 4-quinazolone (60) :

A mixture of benzanthranil (2.6 g, 11.6 mmol) and 85% hydrazine hydrate (15 ml) was refluxed for 2 hours, the clear solution cooled, filtered and recrystallized from alcohol to give 2.2 g (80%) of 60, mp 176°C (lit.[8] mp 177°C).

XII. The reaction of 2-phenyl 3-benzamido 4-quinazolone (61) with aqueous alkali : Isolation of 1-(o-carboxyphenyl) 2,5-diphenyl triazole (62):

2-Phenyl 3-benzamido 4-quinazolone (61).

A mixture of 2-phenyl 3-amino 4-quinazolone (60) (4.6 g, 0 0194mol), benzoyl chloride (2.8 ml, 0.024 mol) and pyridine (20 ml, 0.246 mol) was stirred overnight at rt., poured onto cold water (~ 200 ml), filtered, washed with cold

pathway precisely similar to that of the methyl analog 56.

---

62 : mp : 319-320°C

63 : mp : 208-210°C

ir : ν_{max} (KBr) cm^{-1}; 1720 (-CO)

nmr : δ ($CDCl_3$), 60 MHz : 3.55 (s, 3H, $-COOCH_3$), 7.2-8.0 (m, 14H, aromatic)

m/z : 355 (M^+), 295 (M^+ - COOMe).

The above experiments have shown that either the 2-methyl or 2-phenyl substitution of 3-benzamido 4-quinazolone leads to the expected cleavage of the 3,4-bond in preference to the rupture of the 2,3 linkage encountered in the unsubstituted cases. However, further transformations along the desired pathway (CHART II.C.2) were thwarted because of propensity of the 1-nitrogen to add to the amido function leading to triazoles. It was felt that the latter tendency can be made quite unfavourable by sterically shielding the amide carbonyl.

With this aim 2-phenyl 3-pivaloylamino 4-quinazolone (64) was prepared by the reaction of 2-phenyl 3-amino 4-quinazolone with pivaloyl chloride/pyridine in 50% yields.

water and crystallized from ethyl acetate hexane to give 5 g (74%) of 61, mp 200°C (lit.[11] mp 202°C).

tlc : PhH:EtOAc : 80.20, Rf. 0.4

ir : ν_{max}(KBr) cm^{-1}, 3160 (-NH), 1710 (-CO), 1670 (-CO).

Hydrolysis of 61 :

A suspension of 61 (1.2 g, 0.003 mol) in 1N NaOH (25 ml) was refluxed for 12 hours, the clear solution cooled, the precipitated sodium salt collected, acidified with 2N H_2SO_4 (~ 30 ml), left stirred overnight, filtered and crystallized from hot methanol to give 0.6 g (50%) of 62, mp 319-320°C.

XIII. The reaction of 62 with diazomethane: Preparation of triazole methyl ester 63.

A methanolic solution of 62 was transformed with diazomethane in quantitative yields to 63, mp 208-210°C.

Anal. Cald. for $C_{22}H_{17}N_3O_2$ (Mol. Wt. 355)

C, 74.3; H, 4.7; N, 11.8%

Found : C, 74.5; H, 5.3; N, 11.9%

ir : ν_{max}(KBr) cm^{-1}; 1720 (-CO)

nmr : $\delta(CDCl_3)$, 60 MHz : 3.55 (s, 3H, -COOC$\underline{H}_3$), 7.2-8.0 (m, 14H, aromatic)

m/z : 355 (M^+), 295 (M^+ - COOMe).

XIV. The reaction of 2-methyl 3-amino 4-quinazolone (55) with pivaloyl chloride : Preparation of 2-methyl 3-pivaloyl amino 4-quinazolone (64)

A mixture of 2-methyl 3-amino 4-quinazolone (2.9 g, 0.016 mol), pyridine (1.6 g, 0.02 mol) and pivaloyl chloride (2 g, 0.016 mol) and dry benzene (100 ml) was refluxed for 12 hours, evaporated and the residue chromatographed. Elution with PhH:EtOAc :: 70 :30 gave 2.1 g (50%) of 64, mp 164-166°C.

tlc : PhH:EtOAc :.70 :30, Rf. 0.6

Anal. Cald. for $C_{14}H_{17}N_3O_2$ (Mol Wt. 259)

C, 64.8; H, 6 5; N, 16.2%

Found: C, 64.8; H, 6.0; N, 16.8%

ir : ν_{max}(KBr) cm^{-1}, 3300 (-NH), 1718 (-CO), 1675, 1615

nmr : $\delta(CDCl_3)$, 60 MHz 1 4 (s, 9H, ^{t}Bu), 2.4 (s, 3H, $-C\underline{H}_3$), 7.4-8.5 (m, 5H, aromatic).

XV. The reaction of 2-phenyl 3-benzamido 4-quinazolone (61) with distilled water at 200°C: Isolation of 1,2,5-triphenyl triazole (65), 2-phenyl 4-quinazolone (66), benzamide (67), benzhydrazide(68) and benzanilide (69).

A suspension of 61 (0.3 g, 0.9 mmol) in distilled water (3 ml) was sealed and held at 200°C for 12 hours. Five such

batches so processed were cooled, cautiously opened, extracted with ethyl acetate, evaporated and chromatographed.

Eluent PhH:EtOAc	Compound	Yield (%)	mp	lit.mp	m/z
95:5	69	0.35 g (41)	163-164°C	162-164°C	197 (M^+)
90:10	67	0.1 g (19)	126-128°C	128-129°C	122 $(M+1)^+$
60:40	66	0.08 (8)	229°C	223°C[13]	-
50:50	65	0.1 g (8)	296-297°C	299°C[12]	297 (M^+)
10:90	68	0.09 (15)	110-112°C	112°C	136 (M^+)

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15. Please see section I.E. for general experimental methodology.

VITAE

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Scientific Publications:

1. Synthesis on Templates: Regiospecific Synthesis of Imidazoles, D. Ranganathan and F. Farooqi, Tetrahedron Lett., 25, 5701 (1984).
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